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STUDIES ON THE INTRAVENOUS ADMINISTRATION OF WHOLE BOVINE PLASMA AND SERUM TO MAN*†

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THE search for a satisfactory blood substitute has received a strong stimulus in recent times from its obvious need in military surgery and in civil practice for combating states of contracted blood volume and protein stores.

As indicated by Blalock and Mason,[1] intravenous saline or glucose solutions are of much greater value in prevention than in treatment of shock. The use of pectin,[2] recently reported by Hartman and his co-workers, appears to afford promise for cases of contracted blood volume, but would not supply parenteral protein for nutritional purposes. Sterile human ascitic fluid[3] has been used and apparently can be tolerated, but its supply is obviously limited and its protein content low. The use of acacia,[4] which reached its greatest popularity shortly after the last war, has been shown to produce such undesirable side and delayed effects that in recent years its use has been almost entirely supplanted by whole human blood, serum, or plasma. These, it is generally agreed today, are the most desirable agents for combating surgical shock.

However, the source of human material is limited and its procurement and preparation so expensive as to curtail any broad application. On the other hand, the bovine source of blood from which one might fashion a satisfactory blood substitute is practically unlimited and its usefulness unexplored.

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Animals have been used principally for immune sera of many sorts, employing the horse as the principal donor. Why the bovine family has never been used widely is not clear, but apparently the principal reason is its natural immunity to most infectious diseases. In addition, for technical reasons, the horse is easier to bleed, it can be trained to cooperate, and it is easier to care for and to keep clean. However, these are not valid contraindications for neglecting such a cheap and ready source of blood proteins, which, to date, has never been given a thorough experimental or clinical exploration.

Most immunologists have regarded bovine serum as antigenic and unsafe for intravenous injection into man. When plans for this study were being scrutinized a number of years ago, the chief deterrent to undertaking the investigation was the prevalent impression among immunologists that bovine serum was even more antigenic and less compatible to man than was horse serum. The paucity of factual data on the matter was striking. As related above, it was our inference that the horse rather than the bovine was selected for the preparation of immune sera because of the natural immunity of the bovine to the common pyogenic organisms. We were unable to find factual data supporting the alleged toxicity of bovine plasma. We did find that Shortell, Cotting, and Leary[5] (1916) reported the use of bovine plasma principally in treatment of wounds. Penna and associates[6] reported the successful intravenous and intramuscular use of normal bovine serum in treatment of anthrax.

In previous publications[7, 8] we have reported some of our results with bovine plasma; namely, that it can be given in fairly large amounts to some people and that it is apparently retained by the body. On the basis of skin tests with the various fractions of whole bovine plasma, it appeared that the albumin fraction was the least reactive. Recently Cohn and his associates[9, 10] have succeeded in fractionating whole bovine plasma into its various constituents by fractional precipitation at –5° C. with ethyl alcohol. Purified albumin so obtained is now under clinical trial and preliminary studies seem most encouraging. In a letter to the *Journal of the American Medical Association*, Keys, Taylor, and Savage[11] have outlined their experience with fractionation of animal plasma proteins and feel also that a satisfactory human blood substitute may be fashioned from animal blood. However, since the problem of fractionation of plasma proteins is chiefly a chemical one requiring the background, equipment, and facilities of a well-established physical chemistry laboratory rather than a surgical laboratory, we have confined our efforts to studies of: (1) an evaluation of the usefulness of whole bovine plasma and serum in man, (2) a study of the items contributing to reactions with the use of whole bovine plasma or serum, and (3) the effect on nitrogen balance, of bovine and human plasma proteins administered intravenously to man.

PROCEDURE AND PREPARATION

With the cooperation of Dr. W. L. Boyd, of the department of veterinary medicine, four cows free of tuberculosis and brucellosis were placed at our disposal. Four to 5 liters of blood were obtained from each cow every two weeks. Blood was drawn from the jugular vein using a sterile paracentesis trocar and collected into sterile, 4 liter Erlenmeyer flasks. Latterly, through the generosity of Mr. R. A. Keyer, of the Armour Packing Company of South Saint Paul, Minn., a larger stock was placed at our disposal. At the packing house, blood is drawn aseptically from the jugular vein with the same apparatus immediately after the animals are stunned by a blow on the head and suspended from the ceiling by the hindlegs. If serum is to be obtained, the blood is allowed to clot in the collecting flask, and after twenty-four and forty-eight hours the serum is decanted off from a special outlet at the bottom of the flask into 250 c.c. centrifuge tubes and centrifuged for one-half hour at 2,500 r.p.m. If plasma is to be obtained, sufficient sodium citrate solution is added to make a final concentration of 0.3 per cent, the red blood cells being removed by centrifugation. Sulfanilamide in final concentration of 20 mg. per cent was used as a preservative.

Although the entire process was done aseptically, sera were passed through a Seitz filter using E.K. pads, size 14, then bottled and sealed without exposure to the atmosphere. Cultures on veal infusion and brain broth were sterile five to seven days before the material was used. Difficulty was encountered in filtering plasma through the Seitz filter, while serum passed through readily. In addition, plasma, after standing, precipitates fibrin which must be filtered off before using the material. Frozen plasma was prepared by placing the bottles in the freezing coils of a refrigerator for twenty-four hours and then storing them in the frozen state until used. If left out at room temperature, it melts in about one hour. A flaky precipitate of fibrin remains, which was removed before using by filtration through several layers of sterile gauze.

MODIFICATION OF WHOLE BOVINE PLASMA

In order to eliminate the fibrinogen fraction, serum rather than plasma was used. Subsequently, it was found that whole bovine plasma and serum contain hemolysins and hemagglutinins to human red blood cells of the various blood groups. Partial removal of these by adsorption on human red blood cells is possible and apparently reduced the incidence of reactions.

In adsorbing the bovine serum, fresh human cells doubly washed with normal saline solution are mixed gently with the bovine serum in a ratio of 1:5 by volume, and removed in thirty minutes by centrifuga-

tion. If this time is exceeded, hemolysis occurs usually. Apparently, union of reacting antibodies occurs before hemolysis becomes evident, and if the red blood cells are removed by centrifugation at this time, clear unhemolyzed serum can be obtained, with most of the hemolysins and about 50 per cent of the hemagglutinins removed, as indicated in Table I. For these studies serial dilution of serum with normal saline

TABLE I

TITER OF HEMOLYSINS AND HEMAGGLUTININS IN BOVINE SERUM AND PLASMA TO HUMAN RED BLOOD CELLS BEFORE AND AFTER ADSORPTION WITH HUMAN RED BLOOD CELLS AND KAOLIN

BOVINE PLASMA OR SERUM	BEFORE ADSORPTION WITH HUMAN RED BLOOD CELLS		AFTER ADSORPTION WITH HUMAN RED BLOOD CELLS	
	TITER OF HEMOLYSIN	TITER OF AGGLUTININ	TITER OF HEMOLYSIN	TITER OF AGGLUTININ
Serum 15	1:10	1:20	1:2	1:10
Plasma 15	1:2	1:20	0	1:10
Serum 16	1:10	1:25	1:5	1:20
Plasma 16	0	1:25	0	1:25
Serum 17	1:10	1:25	1:3½	1:25
Plasma 6	1:5	1:25	0	1:10
Serum 7	1:3⅓	1:10	1:2	1:5
	BEFORE ADSORPTION WITH KAOLIN		AFTER ADSORPTION WITH KAOLIN	
Serum 86	1:2½	1:3⅓	1:2	1:5
Serum 95	1:3⅓	1:5	1:3⅓	1:10
Serum 96	1:3⅓	1:10	1:2½	1:5
Serum 97	1:5	1:20	1:5	1:20
Serum 98	1:5	1:20	1:5	1:20

solution and 1 per cent suspension of human red blood cells were used and read macroscopically after one hour of incubation at 37° C. In order to explore the possibility of this adsorption's being specific for the erythrocytes, kaolin was used as the adsorbing medium. As noted in Table I, it failed to decrease the titer of either hemolysins or hemagglutinins. Although the entire adsorption procedure was done aseptically, all adsorbed serum was passed through the Seitz filter and cultured as described above before using.

SELECTION OF PATIENTS AND TECHNIQUE OF INJECTION

Patients selected for trial on bovine plasma and serum have been restricted largely to those with carcinoma, usually inoperable. A preliminary skin test was done on all patients using 0.1 c.c. of 1:10 dilution of serum with normal saline solution. In the main, the only patients to whom we attempted to administer bovine plasma or serum were those in whom only slight or negative skin reactions were manifest. Our preliminary experience indicated that subjects with marked positive skin wheals[7, 8] do not take bovine serum well. Following the skin test, 0.1 c.c. of bovine serum diluted to 1 c.c. with normal saline solution is given intravenously. Several hours later, if no reaction occurred, 1 c.c. diluted to 10 c.c. with normal saline solution was given

intravenously; next day 5 c.c. diluted to 10 c.c. was given, and somewhat later, 50 c.c. diluted to 100 c.c. was given. If no reactions occurred, amounts of 250 c.c. diluted with an equal amount of saline or 5 per cent dextrose solution were given. The rate of administration was slow. The preliminary injections of 1 and 10 c.c. were given in about five minutes. The larger injections were given by gravity drip at a rate of 4 to 5 c.c. per minute. If any untoward manifestations appeared, the injection was discontinued immediately.

RESULTS OF INJECTION

In Tables II to IX are tabulated the results of injection of whole bovine plasma, serum, and adsorbed serum to 120 patients. The reactions of all are summarized in Table X. Patients who did not exhibit untoward immediate symptoms received total amounts of from 300 to 2,500 c.c. in divided doses. Under immediate reactions are included all untoward manifestations the day of injection. About 50 per cent of reactions are febrile in character, usually initiated by a chill one-half to one hour after the start of the injection. Other reactions, such as immediate urticaria, edema of eyelids, flushing of skin, backache, gastrointestinal upsets with diarrhea and/or vomiting, dizziness, and severe anaphylactic reactions make up the remainder.

In the whole plasma (Table II) and serum (Table IV) groups, the incidence of immediate reactions was about the same; namely, 58.3 and 66.6 per cent. Freezing of plasma during storage, as recommended by Strumia and McGraw,[12] does not appear to alter the reactive properties of bovine plasma (Table III) for the incidence of reactions was the same as in the other groups. By employing the technique of adsorbing bovine serum on human red blood cells, the incidence of reactions was materially reduced; namely, to 24.5 per cent in 53 patients. In general, the incidence of reactions was fairly constant regardless of the group of red blood cells used for adsorption. Also, there does not appear to be any correlation between the blood group of recipient and the red blood cell group used for adsorption. From these data, it appears likely that, whatever is adsorbed by the red blood cells is either species specific or nonspecific rather than blood group specific. In order to explore this possibility, kaolin was used as the adsorbing medium. In Table I it will be noted that this does not remove any of the hemolysins or hemagglutinins. Five reactions in 13 patients were observed, an incidence of 38.5 per cent, indicating a result midway between serum adsorbed on various groups of red blood cells and whole untreated serum.

In Tables II to IX, the heading "Total Amount Given" represents the summation of all the material injected, while the heading "Amount Causing Reaction" is the single dose at the time at which reaction

TABLE II

REACTIONS ATTENDING INTRAVENOUS ADMINISTRATION OF WHOLE BOVINE PLASMA

PATIENT	AGE	DIAGNOSIS	BLOOD GROUP	SKIN TEST	TOTAL AMOUNT GIVEN (C.C.)	IMMEDIATE REACTION	AMOUNT CAUSING REACTION (C.C.)	DELAYED REACTION
1. Mr. W. M. (U. H. 681255)	60	Carcinoma of stomach	B	0	900	Flush, dyspnea	200	Urticaria in 4 days
2. Mr. H. S. (U. H. 681983)	68	Carcinoma of stomach	A	0	1,000	None	--	None
3. Mr. A. T. (U. H. 650019)	70	Carcinoma of stomach	A	0	500	None	--	None
4. Mr. P. L. (U. H. 693894)	68	Carcinoma of stomach	A	0	440	None	--	
5. Mr. P. C. (U. H. 684487)	64	Carcinoma of stomach	A	0	245	None	--	None
6. Mr. T. S. (U. H. 641802)	37	Bleeding ulcer	O	0	850	None	--	
7. Mr. H. W. (U. H. 684341)	68	Carcinoma of esophagus	O	0	1,500	None	--	Urticaria in 2 days
8. Mr. B. L. (U. H. 688427)	42	Carcinoma of colon	O	0	1,125	Chill	200	
9. Mr. H. L. (U. H. 666961)	56	Carcinoma of stomach	A	1+	510	Diarrhea; chill; temperature, 103°	250	None
10. Mr. M. K. (U. H. 683236)	78	Carcinoma of lip	B	0	510	Chill; temperature to 105°	250	None
11. Mr. W. W. (U. H. 683078)	72	Carcinoma of neck	A	1+	110	Chill; temperature, 105°	100	None

12. Mr. W. C. (U. H. 679451)	56	Carcinoma of penis	A	1+	650	None	--	None
13. Mr. J. K. (U. H. 612060)	65	Lung abscess	A	0	300	None	--	None
14. Mr. H. L. (U. H. 686526)	64	Carcinoma of pancreas	AB	0	175	Chill; temperature, 101°	150	None
15. Mr. W. M. (U. H. 691429)	66	Carcinoma of mouth		0	155	Chill; temperature, 104.6°	50	General urticaria in 2 days
16. Mr. C. H. (U. H. 694306)	61	Carcinoma of stomach	AB	0	556	Flush of skin	5	General urticaria in 4 days
17. Mr. G. S. (U. H. 694205)	40	Carcinoma of stomach	A	0	556	None	--	None
18. Mr. F. G. (U. H. 694278)	68	Common duct stone	O	0	306	General urticaria	250	General urticaria in 7 days
19. Mrs. H. V. (U. H. 684165)	60	Meleney ulcer		0	206	Pain in chest, backache	150	General urticaria in 6 days
20. Mr. J. N. (U. H. 627438)	62	Hemangioendothelioma of spine	A	2+	180	Pain in chest, dyspnea	150	
21. Mr. H. F. (U. H. 695282)	46	Carcinoma of colon		1+	180	Flush, dyspnea, pain in chest	150	General urticaria in 5 days
22. Mr. H. H. (U. H. 695004)	38	Cord tumor	O	1+	556	None	--	General urticaria in 3 days
23. Mr. F. T. (U. H. 694428)	25	Osteogenic sarcoma	A	1+	106	Chill, backache	50	General urticaria in 5 days
24. Mr. J. B. (U. H. 683375)	71	Carcinoma of rectum, asthma	A	1+	2	Anaphylactic response	2	None

TABLE III

REACTIONS ATTENDING INTRAVENOUS ADMINISTRATION OF FROZEN WHOLE BOVINE PLASMA

PATIENT	AGE	DIAGNOSIS	BLOOD GROUP	SKIN TEST	TOTAL AMOUNT GIVEN (C.C.)	IMMEDIATE REACTION	AMOUNT CAUSING REACTION (C.C.)	DELAYED REACTION
1. Mr. F. J. (U. H. 690458)	63	Carcinoma of esophagus	A	Negative	511	Feeling of constriction in chest	200	None
2. Mr. J. H. (U. H. 691907)	56	Carcinoma of esophagus		Negative	556	None	--	None
3. Mr. R. J. (U. H. 694488)	18	Brain tumor	O	Negative	638	Temperature rise, 100 to 102.6°	250	Urticaria in 6 days
4. Mrs. E. M. (U. H. 695037)	43	Carcinoma of breast	AB	2+	556	None	--	None
5. Mr. A. B. (U. H. 694541)	63	Carcinoma of stomach		2+	556	None	--	Urticaria in 5 days
6. Mr. H. H. (U. H. 693852)	63	Carcinoma of stomach	O	Negative	556	None	--	
7. Mrs. C. H. (U. H. 683532)	64	Carcinoma of rectum	A	Negative	556	None	--	
8. Mrs. P. M. (U. H. 695428)	53	Carcinoma of breast		1+	306	Chill, dyspnea	250	General urticaria in 6 days
9. Miss G. G. (U. H. 695186)	6	Nephrosis	A	2+	76	Dyspnea, asthmatoid respiration	40	None
10. Mr. C. D. (U. H. 681384)	76	Carcinoma of mouth	A	Negative	166	Chill, temperature to 101°	150	
11. Mr. L. S. (U. H. 694211)	67	Carcinoma of rectum	O	1+	556	Chill, nausea, headache	250	General urticaria in 4 days
12. Mrs. A. W. (U. H. 650014)	50	Carcinoma of breast	O	Negative	556	None	--	None
13. Mrs. J. E. (U. H. 595736)		Carcinoma of breast	AB	Negative	41	Dyspnea, asthmatoid respiration	35	
14. Mr. H. W. (U. H. 684194)	36	Brain tumor	A	1+	56	Temperature to 103°, nausea, vomiting	50	None
15. Mrs. A. M. (U. H. 695651)	54	Carcinoma of breast	A	1+	56	Chill, temperature to 104°	50	

TABLE IV

REACTIONS ATTENDING INTRAVENOUS ADMINISTRATION OF WHOLE BOVINE SERUM

PATIENT	AGE	DIAGNOSIS	BLOOD GROUP	SKIN TEST	TOTAL AMOUNT GIVEN (C.C.)	IMMEDIATE REACTION	AMOUNT CAUSING REACTION (C.C.)	DELAYED REACTION
1. Mr. B. H. (U. H. 697067)	70	Papilloma of mouth	O	1+	176	Backache	125	Urticaria
2. Mr. M. B. (U. H. 700837)	69	Fractures	A	2+	56	Chill; temperature, 101°	50	
3. Mr. J. D. (U. H. 699116)	56	Carcinoma of rectum	A	0	281	Flush, chilly	225	Urticaria in 7 days
4. Mrs. E. B. (U. H. 700745)	68	Carcinoma of rectum	A	1+	306	Nausea; chill; temperature, 101°	250	
5. Mr. W. S. (U. H. 700406)	60	Carcinoma of rectum	A	0	361	None	--	None
6. Mr. N. P. (U. H. 699634)	68	Carcinoma of neck	A	1+	306	None	--	Urticaria
7. Mrs. M. A. (U. H. 684967)	71	Carcinoma of breast	B	1+	306	None	--	None
8. Mr. J. M. (U. H. 697807)	65	Choledocholithiasis		2+	306	Chill; slight temperature, 100°	250	Urticaria
9. Mr. O. F. (U. H. 670645)	40	Brain tumor		1+	356	None	--	
10. Mr. E. B. (U. H. 600864)	61	Hemangioma	O	1+	56	Urticaria, vomiting, diarrhea	50	
11. Mr. P. Mc. (U. H. 664242)	50	Carcinoma of mouth	A	2+	56	Urticaria	50	
12. Mr. E. R. (U. H. 697238)	67	Lipoma	O	0	0.1	Anaphylactic response	0.1	
13. Mr. D. E. (U. H. 647331)	27	Osteomyelitis	AB	4+	1.1	Severe pain at site of osteomyelitis in spine	1.0	
14. Mrs. S. M. (U. H. 609973)	74	Osteoma	A	1+	300	None	--	
15. Mr. W. C. (U. H. 699745)	64	Carcinoma of rectum	B	0	56	Vomiting, vertigo, nausea	50	

TABLE V

REACTIONS ATTENDING INTRAVENOUS ADMINISTRATION OF GROUP AB ADSORBED BOVINE SERUM

PATIENT	AGE	DIAGNOSIS	BLOOD GROUP	SKIN TEST	TOTAL AMOUNT GIVEN (C.C.)	IMMEDIATE REACTION	AMOUNT CAUSING REACTION (C.C.)	DELAYED REACTION
1. Mrs. E. C. (U. H. 700278)	68	Carcinoma of breast	A	1+	0.1	Anaphylactic response	0.1	
2. Mrs. G. S. (U. H. 674416)	74	Carcinoma of stomach	O	0	306	None	--	Urticaria in 7 days
3. Mrs. M. J. (U. H. 699567)	62	Carcinoma of ear	O	0	306	None	--	Urticaria in 7 days
4. Mr. W. G. (U. H. 698187)	45	Carcinoma of neck	O	1+	306	None	--	Urticaria in 7 days
5. Mr. A. B. (U. H. 698346)	64	Carcinoma of neck	O	0	6	Vertigo, dizziness	5	None
6. Mr. W. T. (U. H. 697089)	80	Carcinoma of nose	A	1+	81	Urticaria, vertigo	25	Urticaria in 5 days
7. Mr. J. B. (U. H. 700713)	75	Carcinoma of stomach	B	1+	1	Abdominal cramps, flush	1	
8. Mr. E. J. (U. H. 669392)	37	Duodenal ulcer	A	0	306	None	--	
9. Mr. J. C. (U. H. 702374)	68	Carcinoma of stomach	A	0	306	None	--	None
10. Mr. P. O. (U. H. 693715)	46	Brain tumor	A	1+	306	None	--	
11. Mr. R. S. (U. H. 702053)	64	Frozen leg	B	0	306	None	--	Urticaria in 4 days
12. Mr. C. B. (U. H. 700738)	70	Choledocho-lithiasis	A	0	306	None	--	None
13. Mrs. M. L. (U. H. 700940)	52	Carcinoma of breast	O	1+	306	None	--	Urticaria
14. Mrs. L. S. (U. H. 702151)	45	Carcinoma of rectum	AB	0	306	None	--	None

TABLE VI

REACTIONS ATTENDING INTRAVENOUS ADMINISTRATION OF GROUP A ADSORBED BOVINE SERUM

PATIENT	AGE	DIAGNOSIS	BLOOD GROUP	SKIN TEST	TOTAL AMOUNT GIVEN (C.C.)	IMMEDIATE REACTION	AMOUNT CAUSING REACTION (C.C.)	DELAYED REACTION
1. Mrs. E. W. (U. H. 698867)	37	Carcinoma of colon	A	1+	612	Severe backache	1	
2. Mrs. H. S. (U. H. 688054)	54	Duodenal ulcer	A	1+	306	Chill	250	Severe urticaria in 4 days
3. Mr. A. S. (U. H. 698210)	60	Carcinoma of stomach	A	0	306	None	--	Urticaria in 6 days
4. Mr. J. C. (U. H. 698886)	76	Carcinoma of stomach	O	0	306	None	--	None
5. Mr. C. S. (U. H. 698650)	62	Carcinoma of stomach	O	0	306	None	--	Urticaria in 10 days
6. Mr. B. K. (U. H. 698076)	55	Osteomyelitis diabetes	O	0	306	None	--	
7. Mr. J. L. (U. H. 697541)	62	Leukemia	A	1+	306	None	--	None
8. Mr. A. F. (U. H. 628276)	64	Carcinoma of cheek	O	1+	306	None	--	
9. Mr. C. S. (U. H. 698996)	62	Carcinoma of colon	B	1+	306	None	--	None
10. Mrs. A. C. (U. H. 698769)	52	Carcinoma of colon	A	0	306	None	--	Urticaria in 6 days
11. Mrs. E. N. (U. H. 631060)	55	Carcinoma of stomach	O	1+	230	Backache	50	Urticaria
12. Mr. C. S. (U. H. 694547)	54	Carcinoma of stomach	AB	1+	2,400 in 6 days	Pulmonary edema (?); temperature, 101°	300	Urticaria in 3 days
13. Mr. A. W. (U. H. 699335)	54	Carcinoma of stomach	O	1+	56	None	--	None
14. Mrs. J. S. (U. H. 700142)	35	Malignant melanoma	AB	1+	306	None	--	Urticaria in 3 days
15. Mr. H. S. (U. H. 699124)	66	Carcinoma of colon	A	1+	500	None	--	
16. Mr. W. M. (U. H. 700455)	56	Carcinoma of stomach	A	3+	130	Urticaria, dizziness	50	None

TABLE VII

REACTIONS ATTENDING INTRAVENOUS ADMINISTRATION OF GROUP B ADSORBED BOVINE SERUM

PATIENT	AGE	DIAGNOSIS	BLOOD GROUP	SKIN TEST	TOTAL AMOUNT GIVEN (C.C.)	IMMEDIATE REACTION	AMOUNT CAUSING REACTION (C.C.)	DELAYED REACTION
1. Mr. W. S. (U. H. 638490)	64	Carcinoma of neck	B	1+	306	None	--	None
2. Mr. A. J. (U. H. 684304)	56	Hypernephroma	A	1+	306	None	--	None
3. Mr. C. E. (U. H. 699770)	58	Carcinoma of colon	A	1+	306	None	--	Urticaria in 6 days
4. Mr. E. B. (U. H. 662052)	55	Carcinoma of tongue	O	0	306	None	--	None
5. Mr. W. T. (U. H. 699726)	62	Fracture	O	2+	306	Chill; temperature, 103°	250	
6. Mr. W. C. (U. H. 699745)	55	Carcinoma of rectum	O	0	306	None	--	Urticaria in 5 days
7. Mr. R. L. (U. H. 698833)	56	Carcinoma of hand	A	0	306	None	--	
8. Mr. J. K. (U. H. 638854)	80	Carcinoma of prostate	A	1+	306	Urticaria	250	
9. Mrs. A. L. (U. H. 686334)	55	Carcinoma of breast	O	0	361	None		Urticaria in 6 days
10. Mr. E. R. (U. H. 699902)	65	Carcinoma of lip	O	0	306	None	--	None
11. Mr. O. H. (U. H. 702708)	55	Carcinoma of stomach	A	2+	306	None	--	

TABLE VIII

REACTIONS ATTENDING INTRAVENOUS ADMINISTRATION OF GROUP O ADSORBED BOVINE SERUM

PATIENT	AGE	DIAGNOSIS	BLOOD GROUP	SKIN TEST	TOTAL AMOUNT GIVEN (C.C.)	IMMEDIATE REACTION	AMOUNT CAUSING REACTION (C.C.)	DELAYED REACTION
1. Mrs. A. R. (U. H. 700102)	61	Carcinoma of breast	A	0	306	None	--	None
2. Mr. F. F. (U. H. 700490)	47	Carcinoma of colon	O	0	356	None	--	Urticaria in 7 days
3. Mr. M. D. (U. H. 695457)	62	Carcinoma of rectum	O	1+	56	Temperature, 103°; urticaria; chill	50	Urticaria
4. Mrs. S. L. (U. H. 700728)	61	Carcinoma of rectum	A	0	306	None	--	Urticaria in 7 days
5. Mr. J. M. (U. H. 700143)	55	Carcinoma of colon	O	0	306	None	--	None
6. Mr. R. P. (U. H. 660248)	62	Carcinoma of mouth	A	0	306	None	--	
7. Mr. N. M. (U. H. 702113)	72	Carcinoma of face	A	0	306	None	--	None
8. Mr. T. C. (U. H. 700746)	35	Tuberculosis		1+	306	None	--	Urticaria in 4 days
9. Mrs. A. D. (U. H. 691666)	52	Osteomyelitis	A	0	306	None	--	Urticaria in 4 days
10. Mrs. C. H. (U. H. 699318)	40	Carcinoma of stomach	A	1+	306	None	--	None
11. Mrs. M. L. (U. H. 691725)	59	Diverticulosis of colon	O	0	306	None	--	
12. Mr. R. A. (U. H. 703923)	27	Actinomycosis		0	106	Urticaria, diarrhea	50	

TABLE IX

REACTIONS ATTENDING INTRAVENOUS ADMINISTRATION OF KAOLIN ADSORBED BOVINE SERUM

PATIENT	AGE	DIAGNOSIS	BLOOD GROUP	SKIN TEST	TOTAL AMOUNT GIVEN (C.C.)	IMMEDIATE REACTION	AMOUNT CAUSING REACTION (C.C.)	DELAYED REACTION
1. Mr. J. P. (U. H. 705302)	74	Carcinoma of tongue	A	0	46	Chill, temperature to 104°	40	
2. Mr. J. L. (U. H. 705875)	54	Carcinoma of stomach	A	0	56	General urticaria	50	
3. Mr. W. H. (U. H. 705875)	57	Carcinoma of mouth		0	256	Edema of eyelids, gastrointestinal cramps	200	Urticaria in 5 days
4. Mrs. H. G. (U. H. 705359)	71	Carcinoma of rectum	A	0	305	None	--	None
5. Mrs. P. E. (U. H. 702776)	61	Carcinoma of breast	A	1+	306	None	--	
6. Mr. C. L. (U. H. 702930)	60	Diabetic gangrene leg	B	0	56	Nausea, vomiting, vertigo	50	
7. Mr. N. D. (U. H. 703096)	52	Hypernephroma	O	0	131	None	--	
8. Mrs. E. W. (U. H. 703730)	69	Carcinoma of rectum	O	0	56	Temperature to 103°	50	Urticaria
9. Mrs. G. L. (U. H. 705456)	62	Perineal ulcer		0	306	None	--	None
10. Mr. M. M. (U. H. 688186)	62	Carcinoma of pancreas		0	306	None		Urticaria in 10 days
11. Mr. S. K. (U. H. 702881)	60	Carcinoma of rectum	A	0	306	None	--	Urticaria
12. Mrs. L. G. (U. H. 703480)	65	Carcinoma of groin	A	1+	306	None	--	None
13. Mrs. L. N. (U. H. 702832)	56	Retroperitoneal sarcoma	A	2+	306	None	--	None

occurred. It will be noted that the severe, anaphylactic reactions occurred with the smallest doses of material. If a patient tolerates the small initial doses, there is probably no great natural sensitivity. Reactions occurring with the larger doses of bovine plasma were chills, fever, immediate urticaria, flushing of skin, backache, gastrointestinal upsets, and edema of eyelids. In the entire series, three severe anaphylactic reactions occurred (Mr. J. B., Case 24, Table II; Mr. E. R., Case 12, Table V; Mrs. E. C., Case 1, Table V). All exhibited severe collapse with 2 c.c., 0.1 c.c., and 0.1 c.c. respectively. Their skin tests gave no indication of this sensitivity, although Mr. J. B. did give a history of asthma in the past. In all there were marked circulatory collapse, extreme dyspnea, and unconsciousness coming on almost immediately after the injection. All responded to prompt intravenous injection of 0.5 to 1 c.c. of epinephrine, and after fifteen to thirty minutes were back to a fairly normal status. There did not appear to be any sequelae to these reactions. Aside from these three severe reactions, the remainder have been mild to moderate in nature and have not caused us any undue concern. Occasionally amyl nitrite, if given early, was effective in alleviating chills. Histaminase tablets, given by mouth (two tablets t.i.d.) before injections were started, and continued for seven days after injections, did not appear to influence the incidence of either immediate or delayed reactions.

TABLE X

SUMMARY OF REACTIONS WITH BOVINE SERUM AND PLASMA

	IMMEDIATE REACTIONS			DELAYED REACTIONS*		
	NO. OF PATIENTS	NO.	%	NO. OF PATIENTS	NO. OF REACTIONS	%
Whole bovine plasma	24	14	58.3	19	9	47.3
Frozen bovine plasma	15	9	60.0	10	4	40.0
Whole bovine serum	15	10	66.6	6	4	66.6
Human R.B.C. adsorbed serum						
Group AB	14	4	28.5	10	6	60.0
Group A	16	5	31.3	12	7	58.3
Group B	11	2	18.2	7	3	42.9
Group O	12	2	16.6	9	5	55.5
Total	53	13	24.5	38	21	55.3
Kaolin adsorbed serum	13	5	38.5	8	4	50.0

*Not all patients were available to determine that delayed reactions occurred. These figures include only those patients on whom we have definite information.

Delayed reactions characterized by generalized urticaria, edema, and gastroenteritis have occurred in about 60 per cent of patients followed. In general, the incidence was the same in all groups. They usually appeared three to ten days after the final injection and lasted forty-eight to seventy-two hours. Although they were quite distressing to the patients, all recovered within three days. Adrenalin in peanut oil proved to be

the most efficacious agent in relieving these symptoms. No instances of delayed food sensitivity to beef or milk have been observed.

On two occasions bovine plasma was used in treatment of shock. One patient with a bleeding ulcer, whose blood pressure was 80/40, was given 300 c.c. bovine plasma intravenously over an hour's time. The blood pressure rose to 130/90 where it was maintained for the next two and one-half hours while an additional 400 c.c. was given. The other patient, given 500 c.c. bovine serum, exhibited a blood pressure rise from 90/70 to 110/80.

To two patient, 2,500 c.c. and 2,400 c.c. of bovine serum were given in divided doses over a six-day period. In one on a metabolism study (Table XII), there was no untoward effect at the time of injections; the other (Mr. C. S., Case 12, Table VI) developed signs of pulmonary congestion after the last injection, which may have been on the basis of pulmonary edema from increased blood volume. However, the possibility of capillary damage and increased permeability must be borne in mind.

Six patients were given reinjections of whole bovine plasma or serum after variable intervals (Table XI). In this group there were three anaphylactic types of response with small doses of bovine serum relieved by prompt administration of adrenalin indicating a 50 per cent incidence of anaphylactic sensitization. Similarly, in guinea pigs, whole bovine plasma was found to produce the anaphylactic state consistently.

NITROGEN METABOLISM STUDIES

Metabolic studies were made on 3 patients using whole human plasma and on 3 patients using whole bovine plasma or serum. All patients were essentially afebrile. During the period of study, the patients were on a protein-free diet. Tea, orange juice, nectar, and water were allowed by mouth. Enough dextrose solution was given parenterally to maintain a fairly satisfactory caloric intake and to avoid ketosis. Total urinary output was collected, preserved with toluene, and daily determinations of total urinary nitrogen[13, 14] checked by macro- and micro-Kjeldahl methods, nonprotein nitrogen and urea nitrogen[15] were made. At intervals of every two days, blood plasma protein,[13] urea nitrogen,[16] and nonprotein nitrogen[13] levels were determined. The usual procedure was to keep the patient on a preliminary protein starvation regime for four or five days to allow urinary nitrogen to reach a basal level, then to give whole human or bovine plasma intravenously for a five-day period followed by another period of protein starvation.

Table XII illustrates the effect of intravenous administration of bovine serum on nitrogen metabolism. In the basal period, Jan. 3, 1941, through Jan. 8, 1941, this patient did not reach as low a urinary nitrogen excretion as most of our studies have shown. Usually after ade-

TABLE XI

REACTIONS ATTENDING SUBSEQUENT INJECTIONS OF BOVINE PLASMA OR SERUM

PATIENT	ORIGINAL INJECTION				SUBSEQUENT INJECTION			
	DATE	SKIN TEST	AMOUNT GIVEN (C.C.)	REACTION	DATE	SKIN TEST	AMOUNT GIVEN (C.C.)	REACTION
Mr. D. G. (U. H. 684487)	9/5/39-9/6/39	Negative	275	None	10/24/39	Negative	25.0	None
Mr. W. M. (U. H. 681255)	7/7/39-7/10/39	Negative	800	Dyspnea, skin flush	7/18/39	Negative	100.0	None
Mr. J. C. (U. H. 648201)	8/29/39	Negative	25	None	9/5/39	Negative	50.0	None
Mrs. G. L. (U. H. 705456)	2/21/41-2/23/41	Negative	306	None	4/2/41	2+	3.0	Anaphylactic response with marked dyspnea, pain in chest, vertigo
Mr. F. T. (U. H. 694428)	5/14/40-5/15/40	1+	400	Chill, temperature to 103°	4/1/41	1+	1.0	Anaphylactic response, dyspnea, vertigo, extreme apprehension
Mr. W. H. (U. H. 705875)	3/8/41-3/10/41	Negative	256	Edema of eyelids	4/7/41	2+	2.5	Anaphylactic response, dyspnea, pain in chest

TABLE XII

NITROGEN BALANCE STUDIES ATTENDING INTRAVENOUS ADMINISTRATION OF BOVINE SERUM*

PERIOD	URINE			BLOOD			DAILY CALORIC INTAKE	NITROGEN INTAKE AS BOVINE SERUM INTRAVENOUSLY (C.C.)	WEIGHT (KG.)
	TOTAL N_2 (GM.)	N.P.N. (GM.)	UREA N_2 (GM.)	TOTAL PROTEIN (GM.)	N.P.N. (MG. %)	B.U.N. (MG. %)			
1/3/41-1/8/41	47.32	47.22	28.54	5.62	23.0	10.5	1,500	0	51.8
Average daily	7.88	7.86	4.91						
1/9/41-1/13/41	34.55	34.51	17.28	6.19	23.3	15.0	1,500	2,500 Total N 30.75 Gm. Average daily 6.15 Gm.	51.8
Average daily	6.91	6.90	3.46						
1/14/41-1/17/41†	25.80	25.37	13.73	5.95	32.0		1,500	0	51.3
Average daily	6.45	6.34	3.43						

*Mr. O. W. (U.H. 702623), aged 48 years, carcinoma of colon.

†Patient developed general urticaria and edema lasting 2 days, from 1/15/41 to 1/17/41.

TABLE XIII

NITROGEN BALANCE ATTENDING INTRAVENOUS ADMINISTRATION OF HUMAN PLASMA*

PERIOD	URINE			BLOOD			AVERAGE DAILY CALORIC INTAKE	NITROGEN INTAKE AS HUMAN PLASMA INTRAVENOUSLY (C.C.)	WEIGHT (KG.)
	TOTAL N_2 (GM.)	N.P.N. (GM.)	UREA N_2 (GM.)	TOTAL PROTEIN (GM.)	N.P.N. (MG. %)	B.U.N. (MG. %)			
9/9/40-9/12/40	25.04	24.96	17.17	6.03	28.2	14.7	600	0	45.0
Average daily	6.26	6.24	4.29						
9/13/40-9/17/40	21.88	22.00	13.80	6.09	26.0	14.7	600	2,500 Total N_2 28.0 Average daily 5.6	44.2
Average daily	4.37	4.4	2.76						
9/18/40-9/22/40	16.95	16.97	9.53	6.38	30.3	11.2	1,000	0	44.3
Average daily	3.39	3.39	1.90						

*Mr. J. O. (U. H. 695929), aged 51 years, carcinoma of colon.

quate starvation, the urinary nitrogen reaches levels of 3 to 4 Gm. daily. Following this initial starvation period, 500 c.c. of adsorbed bovine serum was given intravenously daily. Total nitrogen analysis of this serum showed 1.23 Gm. per 100 c.c. (7.68 Gm. protein per 100 c.c.). Although positive nitrogen balance is not attained, it is noted that the average daily urinary nitrogen excretion decreased during this period over the basal period (6.91 Gm. nitrogen to 7.88 Gm. nitrogen) while 30.75 Gm. of nitrogen in the form of plasma protein was given intravenously. No protein appeared in the urine. In the subsequent period of nonprotein intake, there was no delayed spillage of nitrogen as indicated by an average daily excretion of 6.45 Gm. nitrogen. There was a slight increase of the plasma protein level from 5.62 at the end of the initial starvation period to 6.19 Gm. per 100 c.c. at the end of the injection period. Also, there did not appear to be any shift of the urea nitrogen-nonprotein nitrogen ratio which might indicate an abnormal catabolism of protein. It would appear, therefore, that this protein, given intravenously to man, is certainly retained by the body for nitrogen metabolism or for replenishment of protein stores.

In a similar study using whole human plasma (Table XIII), positive nitrogen balance was obtained in three consecutive cases. During the starvation period, Sept. 9, 1940, through Sept. 12, 1940, there was an average daily urinary nitrogen excretion of 6.26 Gm. In the five-day period, Sept. 13, 1940, through Sept. 19, 1940, when 2,500 c.c. of whole human plasma containing 28 Gm. nitrogen was given intravenously, only 21.88 Gm. of nitrogen appeared in the urine, or an average daily urinary nitrogen excretion of 4.37 Gm. In the subsequent starvation period, the average daily nitrogen excretion was 3.39 Gm. nitrogen, indicating that the plasma protein injected intravenously is retained by the body. Since there was no significant rise in the plasma protein level of the patient, while an amount of plasma protein about equal to his total circulating plasma protein was given, this must have been taken out of the circulation and used for nitrogen metabolism or for replenishing the protein stores. Pommerenke and co-workers[17] have reported maintenance of dogs in positive nitrogen balance by intravenous administration of dog plasma but failed to note utilization of a heterologous protein (horse serum) in dogs.

DISCUSSION

Bovine plasma and serum can be given to man and even though its use has been attended with a high incidence of reactions, in only 3 out of 120 patients were the reactions of such magnitude as to jeopardize the life of the recipient. In our hands there have been no fatalities. These three severe anaphylactic reactions occurred with small doses, 0.1 c.c., 0.1 c.c., and 2 c.c. of bovine serum or plasma and appeared almost immediately. All responded to prompt intravenous administra-

tion of epinephrine in amounts of 0.5 to 1 c.c. The other reactions of less severe magnitude occurred with larger doses and appeared at variable times after the start of the injection or even several hours after the completion of the injection. If a patient tolerates the small initial doses, there is probably no great natural sensitivity, and the reactions to a larger dose are not of such severe nature. Although the incidence of reactions was reduced from 66.6 per cent with whole serum to 24.5 per cent by adsorption with human red blood cells, their incidence and magnitude were still sufficient to contraindicate any clinical use of whole bovine serum or plasma at the present time. Also, this modification does not insure against the anaphylactic type of reaction for one of the three cases was in the adsorbed group.

The reaction that occurs with adsorption by human red blood cells apparently is not specific to the various groups of red blood cells or to the blood group of the recipient, but the adsorption may remove a species specific substance in the bovine serum capable of producing untoward symptoms in a foreign host. It is not likely that removal of hemolysins, as such, is an important factor in reactions, as they are not present in sufficiently high concentrations to be active, when diluted in the blood stream of the recipient, and reactions, when they did occur, were not attended by jaundice or hemoglobinuria. A more likely possibility, therefore, would be that adsorption removes some reaction-producing substance in addition to, or as a corollary of, removing hemolysins and hemagglutinins. This explanation may account satisfactorily for the observation that kaolin, although its use reduced the incidence of reactions somewhat, was not as effective an adsorbing agent as red blood cells.

One might surmise that with the added experience and improvement in technique of preparation of plasma and serum gained over a period of eighteen months, the latter products would reflect a lower incidence of reactions. Hence the results with adsorbed serum might be interpreted as more apparent than real. However, this was not the case, for the results with the use of whole bovine serum, also prepared in the latter months of this study after the technique of preparation was well standardized, do not show a similar improvement over our earlier experiences when plasma was used.

Delayed reactions of the serum sickness type were a frequent occurrence in our series, occurring in 43 of 81 patients followed. There did not appear to be any very significant difference in its incidence in any of the groups studied. Very few joint manifestations were noted, the principal complaints being urticaria with occasional gastrointestinal upsets and low-grade fever. The onset varied from two to ten days after the final injection, and symptoms subsided usually after forty-eight to seventy-two hours. It is of interest that no instance of serum sickness occurred until serum or plasma injections were discontinued.

Apparently repeated daily injections of bovine serum for six or seven days prevented the onset of serum sickness until cessation of injections after which it appeared in several days.

It would appear that the use of bovine plasma proteins in clinical states of shock or depleted protein stores may have real value, in those patients who can tolerate it, to provide a source of parenteral nitrogenous alimentation as well as to combat the contracted blood volume of shock. Further trial with preparations of bovine albumin may eliminate reactions sufficiently to establish the albumin fraction of bovine plasma as a safe and practical blood substitute for the treatment of contracted blood volume and protein states in man. As yet, however, the injection of bovine plasma or one of its fractions must be looked upon as an experimental project.

SUMMARY

1. Our experiences with the use of whole bovine serum and plasma in 120 patients are reported. The incidence of reactions was sufficient to contraindicate any clinical use of whole bovine serum or plasma at the present time.

2. Bovine plasma and serum are shown to contain hemolysins and hemagglutinins to human red blood cells. Most of the hemolysins and about 50 per cent of the hemagglutinins can be removed by adsorption on human red blood cells. By so doing, the incidence of reactions was reduced from 66.6 to 24.5 per cent.

3. Positive nitrogen balance can be attained by intravenous administration of human plasma and can be approached closely with intravenous administration of whole bovine plasma. Both are apparently retained and utilized by the body.

4. The preparation of a satisfactory product of bovine albumin, from which the globulin fraction has been eliminated completely, may prove a safe and practical blood substitute.

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A COMPARISON OF THE EFFECTS OF THE LOCAL APPLICATION OF HEAT AND OF COLD IN THE PREVENTION AND TREATMENT OF EXPERIMENTAL TRAUMATIC SHOCK

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IN A PREVIOUS paper[1] the effects on animals in shock of causing rather pronounced elevations or depressions of the body temperature by the general application of heat or cold were reported. It was noted that significant elevations of temperature decrease the chance of life and shorten the period of survival. The application of cold does not increase the chance of survival but is accompanied with a lengthening of the survival of an animal with a low blood pressure. The studies showed that significant elevations above normal of the temperature of animals in shock cause more disastrous effects than do depressions of similar degree. It was pointed out that in shock there is not an identical reduction in the flow of blood to all tissues, that the flow to the extremities is more reduced than that to the more vital structures, and that the causation of general peripheral vasodilatation by the application of heat may result in harmful effects. It was concluded that vigorous efforts to elevate the body temperature should not be undertaken in secondary shock unless at the same time one causes an increase in the blood volume by the introduction of whole blood or a suitable substitute for it.

In the previous experiments[1] the application of heat or cold was general. In the present studies, in which shock was produced by gross trauma to an extremity, the application of heat or cold was limited to the injured part and an effort was made to compare the effects of the two agents. In this connection it is to be noted that Allen[2] found that constriction of the circulation of the thigh is more likely to be followed by the development of shock if the temperature is high than if it is low.

METHODS AND RESULTS

Large animals were used in all experiments. Pain was prevented by the use of suitable anesthetic agents: nembutal 25 to 30 mg. per kilogram of body weight in some experiments, barbital 0.3 Gm. per kilogram of body weight in some, and morphine supplemented by the inhalation of ether during the period of traumatization in others. An additional dose of the anesthetic agent was administered if the degree of the anesthesia became light. The method which was used for producing shock

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consisted in striking one of the posterior extremities a number of blows with a blunt instrument. After the trauma had been produced the injured extremity was surrounded by ice packs in approximately one-half of the experiments and by bags containing hot water in the others. The blood pressure was determined by arterial cannulation and the use of a mercury manometer. The hematocrit determinations were made by the use of Van Allen tubes. The locations in which temperature readings were made in most of the experiments included the rectum, the peritoneal cavity (through a small stab incision), and the subcutaneous tissues of the axilla and of the injured extremity. In most instances the animals were observed until death occurred, and the loss of blood and fluid into the injured part and the adjacent tissues was determined by the bisection method which has been described previously.[3] The experiments are divided into groups according to the anesthetic agent that was used.

Nembutal Anesthesia.—

1. Application of Heat: Fourteen experiments of this type were performed. The average duration of life was five hours and fifty-two minutes, and the average difference in the weights of the traumatized and nontraumatized parts was 3.80 per cent of the body weight. The average elevations of temperature were as follows: rectal, +5.7° F.; peritoneal cavity, +6.7° F.; axillary, +4.8° F.; and injured leg, +7.6° F.

2. Application of Cold: There were seventeen such experiments. One of the animals did not develop shock and was killed after twenty-two hours, the difference in the weights of the two posterior parts being 2.83 per cent of the body weight. In the remaining sixteen experiments the average duration of life was thirteen hours and thirty-two minutes, and the average difference in the weights of the traumatized and nontraumatized parts was 3.98 per cent of the body weight. The average depressions of the temperature were as follows: rectal, –15.8° F.; peritoneal cavity, –5.9° F.; axillary, –7.0° F.; and injured leg, –48.0° F.

Barbital Anesthesia.—

1. Application of Heat: Six experiments of this type were performed. The average duration of life was five hours and forty-four minutes, and the average difference in the weights of the injured and noninjured parts was 4.05 per cent of the body weight. The average elevations of temperature were as follows: rectal, +4.9° F.; peritoneal cavity, +6.6° F.; axillary, +4.7° F.; and injured leg, +8.0° F.

2. Application of Cold: There were six experiments of this type. The average survival period was eight hours and fifty-four minutes, and the average difference in the weights of the injured and noninjured parts was 3.58 per cent of the body weight. The average depressions of temperature were as follows: rectal, –12.2° F.; peritoneal cavity, –10° F.; axillary, –10.0° F., and leg, –45.8° F.

Morphine-Ether Anesthesia.—

1. Application of Heat: There were five experiments of this type. The average survival period was five hours and fifty minutes, and the average difference in the weights of the two parts was 3.40 per cent of the body weight. The average elevations of temperature were as follows: rectal, +5.3° F.; and peritoneal cavity, +6.5° F.

2. Application of Cold: There were seven of these experiments. The average survival period was eight hours and thirty-nine minutes, and the average difference in the weights of the injured and noninjured parts was 3.73 per cent of the body weight. The average decline of the rectal temperature was −8.8° F., and that of the temperature of the peritoneal cavity was −3.1° F.

If the groups are combined, the differences in anesthetic agents being ignored, there were twenty-five experiments in which heat was applied locally following trauma to an extremity and twenty-nine experiments in which cold was applied. The following results were obtained: Average survival periods: (1) heat, 5 hours and 49 minutes; and (2) cold, 11 hours and 24 minutes. Average differences in weights of traumatized and nontraumatized parts in percentages of body weight: (1) heat, 3.78; and (2) cold, 3.84. Average alteration in temperature in degrees Fahrenheit: rectal, (1) heat, +5.4, and (2) cold, −12.7; peritoneal cavity, (1) heat, +6.6, and (2) cold, −6.1; axilla, (1) heat, +4.8, and (2) cold, −7.8; injured leg, (1) heat, +7.7, and (2) cold, −47.4.

It should be noted that the local applications of heat and of cold were made to the injured extremity and thus the temperature of the part would be expected to be altered greatly, as was the case. Furthermore, the containers which held the hot water or the ice were in fairly close proximity to the rectal region and undoubtedly there was some direct effect on the rectal temperature. The most significant readings are probably those which were recorded in the peritoneal cavity. It is of interest that the temperature of the abdominal cavity increased slightly in several of the experiments in which ice was applied to an extremity.

Alterations in the hematocrit readings were not great in any of the experiments. There was usually a slight increase in the concentration of the red blood corpuscles in the studies in which heat was applied and a slight dilution in the experiments in which cold was applied. These results suggest that the heat caused an increase in capillary permeability.

COMMENT

Before these experiments were undertaken it was hoped that the local cooling of the injured part would lessen the escape of blood and fluid into the traumatized area and the adjacent tissues. The results do not indicate that such is the case since the loss in these studies was almost identical with that noted in the experiments in which heat was applied. It is possible that the escape of fluid into the injured tissues would have been lessened had the part been cooled more rapidly.

It is of interest that the average survival period of the animals in the group in which cold was applied was twice that of the group in which an elevation of body temperature was caused by the local application of heat. The results are similar to those reported previously by Mason and myself[1] on the effects of the general application of heat and cold.

Emphasis is to be placed on the fact that these experiments offer no evidence whatever that shock should be treated by causing a depression of the body temperature. The experiments do show very clearly that the survival time is shortened by the local application of heat which is of sufficient degree to cause a marked general elevation of the body temperature. It is likely that a marked rise in the temperature of the tissues is accompanied by vasodilatation and an increase in capillary permeability. It would appear that one is warranted in concluding that extreme degrees of heat should not be used even locally in the treatment of shock, particularly if means are not immediately available for increasing the blood volume by the introduction of blood or a suitable substitute.

It is probably unnecessary to mention the fact that the experimental conditions reported here may be somewhat different from the conditions that are present in shock in man. The response to alterations in temperature may be somewhat different in animals and in man. Dogs dissipate heat, in the main, by panting. In these studies anesthesia was necessary, whereas this complicating factor may not be a part of the picture in traumatic shock in patients. Furthermore, the temperature of the animals was normal at the beginning of the experiments, whereas exposure to inclement weather may have lowered the temperature of the patient. It is agreed that the patient who has been exposed to cold and moisture should be placed in a warm bed and should be covered with blankets. On the other hand, the indiscriminate use of large numbers of hot-water bottles and other heating devices may result in harm rather than in improvement in the general condition of the patient.

It is a pleasure to express my thanks to Dr. Barney Brooks for his helpful advice.

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A STUDY OF GASTROINTESTINAL MOTILITY IN THE DOG FOLLOWING ILEOCOLOSTOMY AND PARTIAL COLONIC RESECTION

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THE rationale upon which the anastomotic procedures of the ileum and colon are based is that by diversion of the fecal stream past the site of pathology, physiologic rest will be attained. The benefits to be accrued from this include subsidence of inflammatory reactions localization of infectious processes, decreased absorption of toxic products from the involved segment, relief from obstruction, decompression, and general rehabilitation in preparation for further surgery.

The procedure of ileocolostomy has been recommended for a multitude of pathologic processes involving the right half of the colon and the terminal segment of the ileum. The anastomosis alone has been advocated as a curative procedure in some instances; in others, it is recommended as the first stage in preparation for resection of the right half of the colon. Lewison,[1] Colp,[2] Berg,[3] Crohn,[4] and others have been advocates of ileocolostomy as the surgical procedure of choice in the treatment of regional (segmental, terminal) ileitis. Colp has utilized it for treatment of regional colitis, and many others have long used it for tuberculosis of the ileocecal region and for obstructive lesions of the terminal ileum. Rankin and Graham[5] and Lahey[6] favor completion of an ileocolostomy in preparation for resections of the right half of the colon, and the former have described an aseptic technique for its completion.[7]

A fair amount of clinical evidence exists to indicate that short-circuiting operations upon the ileum and colon do not actually lead to physiologic rest of the proximal colon left behind. Case[8] in 1915 reviewed approximately forty cases of ileocolostomy performed by different surgeons and observed retrograde passage of a barium meal into the blind loop of the colon to be the rule. He frequently noted that the barium content in that area frequently became impacted and that occasionally dilatation of the terminal resected ileum progressed to a point where it assumed the size of the colon. Furthermore, because of the case with which barium enemas regurgitated into the ileum following the anastomosis, he urged the necessity for the reconstruction of a sphincteric mechanism at the site of the new anastomosis. Ginzburg, Colp, and

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Sussman[2] reviewed the roentgenograms of thirty-two cases of ileocolostomy and although they found regurgitation of ileal contents into the excluded segment of colon, this did not lead to abnormal distention, dilatation, or ulceration. Berg[3] recognized that an ileosigmoidostomy did not divert the fecal stream because of continued retrograde peristalsis and accordingly recommended division of the sigmoid at a point proximal to the anastomosis, followed by a resection of the entire excluded colon at a subsequent date.

However, there is little or no experimental work to clarify the question of whether short-circuiting procedures of the colon produce physiologic rest. In addition to that question, there is much more to be learned concerning the fate of the blind loop of colon and the stump of ileum, the effect of pouring liquid feces into the distal portions of the colon, the effects of such procedures on colonic filling and emptying, the compensatory function of the distal colon following resection of one-half or more of the colon, and finally, the influence of these procedures upon the general body economy of the animal.

METHOD

A colony of eleven large, carefully selected, healthy normal dogs were selected and prepared for chronic experimentation. Each animal had an individual kennel, was fed individually, and was given antihelminth medication upon arrival (tetrachlorethylene-magnesium sulfate). Feedings of a standard quantity and quality diet* were given at 9:00 A.M. daily and the animals permitted in outdoor kennels after eating for exercise and defecation. The beneficial effects of this type of care on the general condition of the animal and on the surgical risks were obvious. The animals were trained to lie quietly on a fluoroscopy table.

At weekly intervals, the dogs were fed a barium meal at the time of the usual meal, and the animals fluoroscoped at hourly intervals thereafter for the remainder of that day (eight to nine hours). Records of the passage of the barium meal were kept on specially prepared mimeographed sheets (Fig. 3) and the amounts of barium present in the stomach, small intestines, and colon at each observation were recorded in percentage of the total. The barium meal consisted of 70 Gm. of barium sulfate, mixed well with 150 c.c. of water and one 16 ounce can of dog food.† On the second day the dogs were fed their usual meal at the customary hour, allowed to defecate, and then fluoroscoped at intervals until all barium was evacuated. Usually, eating of the second meal served as the stimulus for complete evacuation of all barium accumulated in the colon overnight.

*A standard meal included the following: One 16 ounce can of commercial dog food, one 12 ounce glass of milk, five slices wheat bread, one tablespoon cod-liver oil, one-half tablespoon powdered brewer's yeast, one teaspoon bone meal.

†The meal was eaten by the animals avidly. This is important, because results are irregular when a barium meal is given by stomach tube.[9]

RESULTS

Normal Controls.—Fifty-two motor meal studies were made at weekly intervals on eleven normal dogs. Fig. 3 is a presentation of the average rate of progress of the barium meals in all dogs. Variations between different animals proved no greater than variations in the same animals, which were slight, so that the values given in Fig. 3 represent results seen in the great majority of instances.

Gastric emptying usually commenced from within one-half to one hour after giving the meal, and emptying was complete between six and eight hours. The small intestines never contained more than 40 per cent of the barium at any time and the barium usually traversed it from seven to nine hours after the eating of the meal. The normal colon began to fill with barium between the fourth and sixth hour and was completely filled at the eighth or ninth hour. Depending upon the habits of the individual animal, some were inclined to defecate barium as soon as the colon began to fill, whereas the majority retained the barium in the colon until permitted outdoors to defecate. Upon defecation, the distal colon emptied itself first, followed by an immediate passage downward of the contents of the proximal colon into the distal portions. Evacuation was usually complete in twenty-four to thirty hours, especially following the eating of a second meal. These studies served as the preoperative controls.

The progress of barium through the gastrointestinal tract of the dog compares very favorably with figures given for the human being by Brown and Sampson.[10]

Barium enemas were given to the same animals to determine the degree of colonic filling and the competency of the ileocecal sphincter. These studies were intended to serve as controls for the barium enemas to be given following ileocolostomy. The enemas were administered under measured pressure from a bottle, attached to which was a pressure bulb and a tycos manometer for measuring the pressures attained.

In only three of the eleven dogs were the ileocecal sphincters consistently competent against regurgitation of the enema under slight pressure. The colon would frequently hold between 600 and 900 c.c. of solution, depending upon the size of the animal. Intracolonic pressures attained for a period of several minutes varied between 30 and 50 mm. In over 70 per cent of the animals the sphincter "gave" at this pressure. The pressure within the colon usually fell when regurgitation into the ileum occurred. It must be appreciated that such pressures are not normally developed, except perhaps under conditions of mechanical obstruction. Evacuation of the barium enema from the colon was usually complete; regurgitated material left the ileum in about the same length of time as in the case of a meal.

Observations Following Ileocolostomy.—End-to-side ileocolostomies were performed under aseptic operative conditions on all eleven dogs under intravenous nembutal (pentobarbital) anesthesia, with two deaths (18 per cent mortality). Figs. 1 and 2 illustrate the procedure employed. We have combined the end-to-side ileocolostomy as described by Rankin and Graham[5, 7] with the aseptic technique of gastrointestinal anastomoses as described by Wangensteen.[11] Division of the ileum was made at a point 5 to 8 cm. distant from the ileocecal junction, for at this level of the ileum there is frequently a branch of the cecal artery and vein which courses along the antimesenteric border of the ileum of the dog; it was utilized to increase the collateral blood supply of the anastomosis.

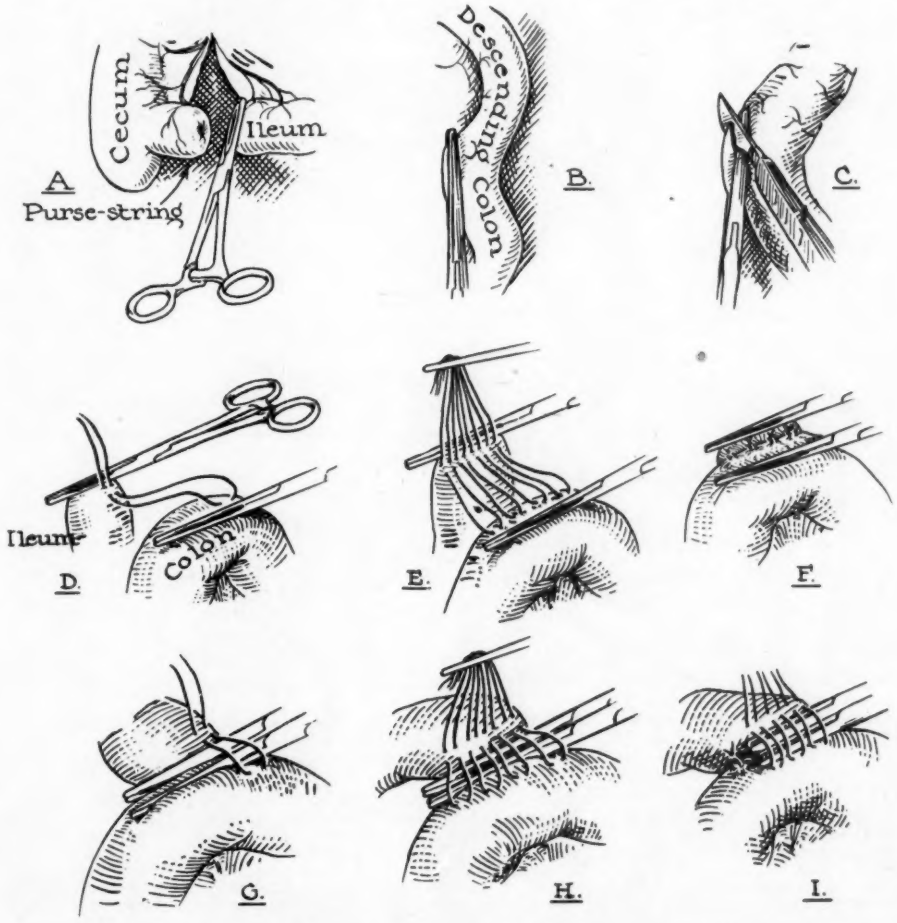

Fig. 1.—Author's modification of end-to-side ileocolostomy. *A*. Ileum severed 5 to 8 cm. distal to ileocecal juncture to take advantage of branch of ileocecal artery usually seen on antimesenteric surface of ileum at this level (not shown in this drawing). *B*. Stoma on colonic side of anastomosis created by clamping small nipple on antimesenteric border. *C*. Nipple removed with scalpel; cauterization with phenol and alcohol. *D*. First interrupted Halsted mattress suture with No. 00.00 intestinal catgut on posterior surface. Sutures placed in longitudinal axis of intestine and stitch on colon twice as large as on ileum to overcome disproportion between circumference of ileum and colon. Four such sutures are adequate (*E*). *F*. Posterior row of interrupted sutures. *G*. and *H*. Four similar sutures constitute anterior row. *I*. Inversion of anastomosis accomplished one suture at a time by gradually withdrawing clamps to free that amount of ileum and colon at a time. In this way a continuously closed anastomosis is assured.

Inversion of the distal ileal stump was accomplished by a purse-string suture of No. 0000 intestinal catgut followed by three or four interrupted Halsted mattress sutures of silk which inverted the first row of sutures. The last silk suture was taken through the undersurface of the cecum to bring it down as a hood over the inverted ileum. The anastomosis of the end of the ileum to the site of the colon was accomplished with two straight-bladed intestinal clamps of small enough caliber to minimize

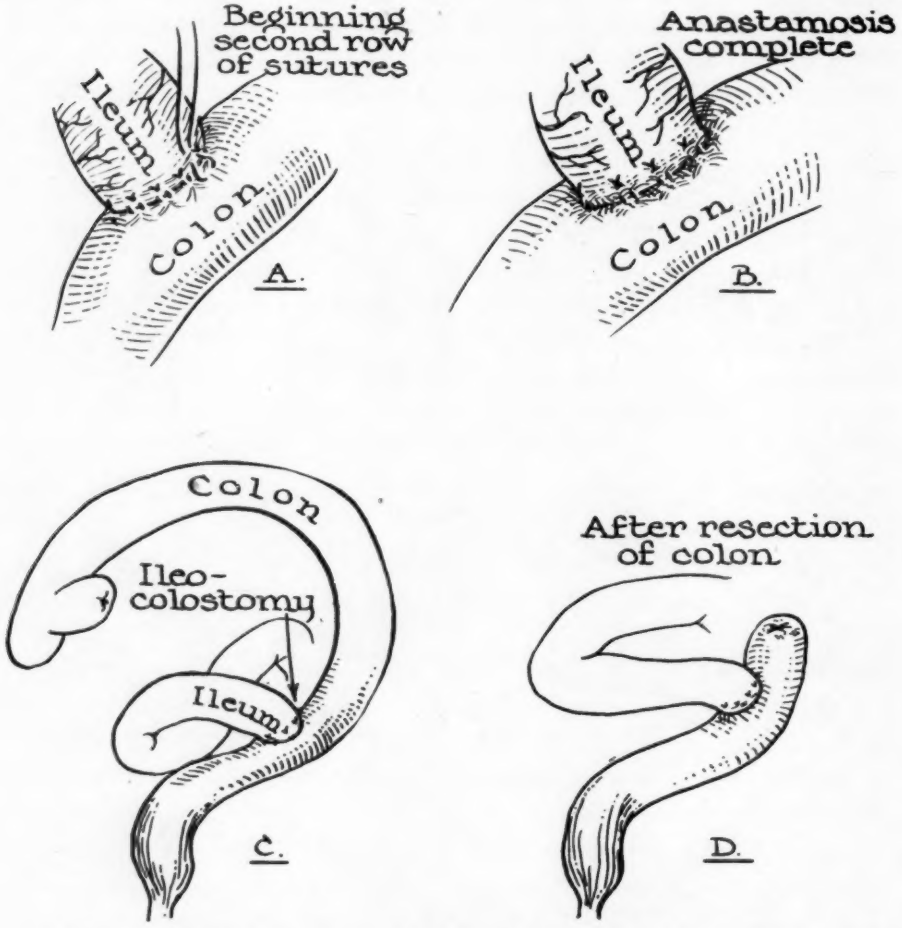

Fig. 2.—*A.* Second row of interrupted Halsted mattress sutures of silk are placed around the circumference of the anastomosis, inverting the previous row of catgut sutures. *B.* The completed anastomosis. *C.* The postoperative appearance of the ileum and colon. The anastomosis is usually wrapped in omentum. *D.* The appearance of the ileum and colon after resection of the proximal excluded colon. Inversion of the severed colon accomplished by the same method used for the anastomosis.

the amount of intestine crushed. The first posterior rows of sutures usually consisted of four interrupted Halsted mattress sutures of No. 0000 intestinal catgut on a small curved atraumatic needle. (Fig. 1.) The sutures were taken along the long axis of both structures, that on the colonic side incorporating about twice as much tissue to overcome the disproportion in the size of the two structures. Similar sutures were

then placed on the anterior surfaces and tied as the two intestinal clamps were gradually withdrawn. A second and final row of similarly interrupted sutures of fine silk were then taken around the circumference of the entire anastomosis. (Fig. 2.) The advantages of the interrupted sutures in this procedure over the continuous sutures as originally described by Rankin[7] lies in the ability to withdraw the intestinal clamps gradually instead of risking spillage of intestinal content as we have frequently otherwise noted. It further decreases the amount of encroachment upon the caliber of the anastomosis, and provides the greater safety inherent in the use of interrupted sutures. Approximately 2 Gm. of

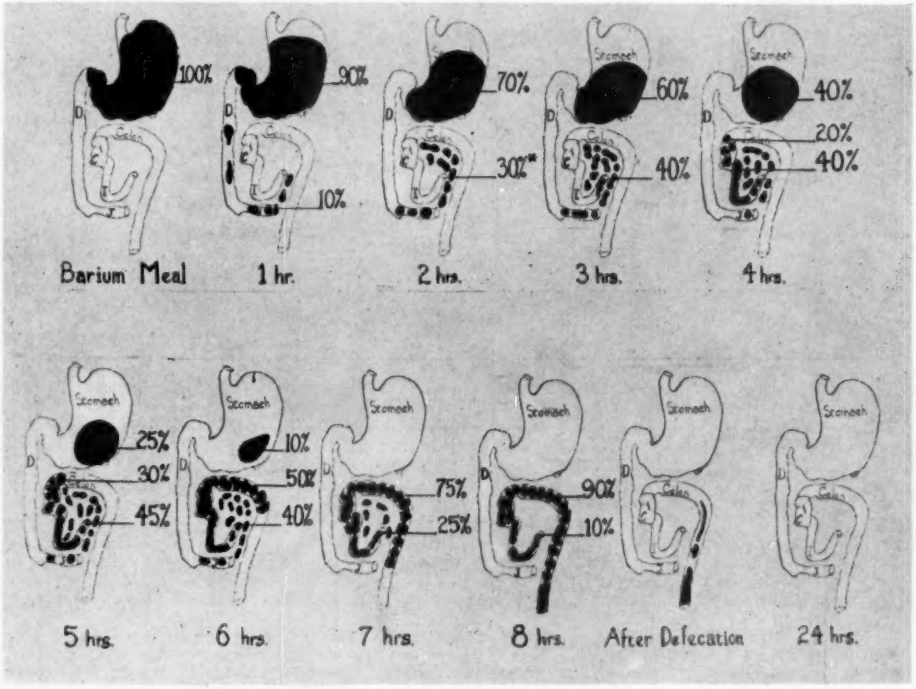

Fig. 3.—Record of average progress of motor meal in normal control dogs as drawn from fluoroscopy. Note that normal colon begins to fill between the fourth and sixth hours and is almost completely filled by the eighth hour. Colon is usually emptied after twenty-four hours if defecation is encouraged by eating. Asterisk denotes percentage of barium in small intestines.

sulfanilamide powder was applied to the serosal surface of the anastomosis, the anastomosis wrapped in omentum and returned to the peritoneum, and closure effected in layers. All animals were given intravenous fluids postoperatively as needed, usually until the third day. Sulfanilamide solution (0.8 per cent in saline solution) was administered subcutaneously for the same period of time. Fluids by mouth were usually begun on the second postoperative day. By the end of the week the animals were returned to their usual diet which they consumed with great appetite. No immediate postoperative complications were en-

countered. After the first week, all stools were formed and were normal in color and character. An interval of at least two weeks elapsed between operation and the first barium meal.

A total of fifty-four barium meal studies were carried out at weekly intervals on the nine dogs which survived the operation. Fig. 4 is a composite representation of the average progress of all barium meals in all dogs following ileocolostomy. The most striking observation was the effect of ileocolostomy upon the time of filling of the colon; whereas in the normal controls this occurred between the fourth and sixth hours,

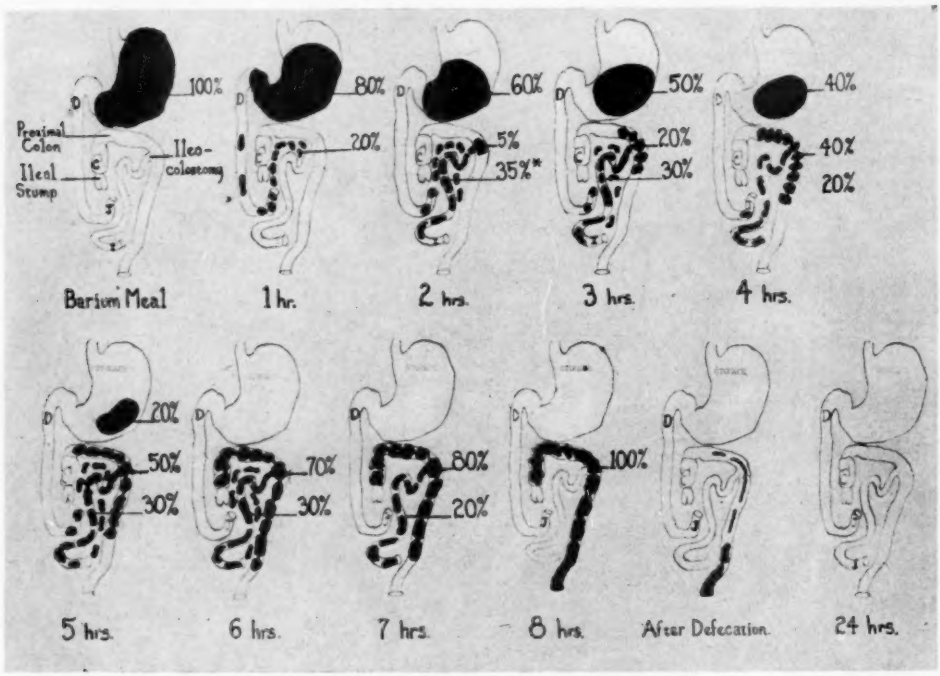

Fig. 4.—Record of average progress of motor meal in same series of dogs as represented in Fig. 3 following ileocolostomy, as drawn from fluoroscopy. Note that gastric emptying time is shortened slightly. Colonic filling commenced two hours earlier than in the normal control and was completed by the sixth hour. Note especially that retrograde passage of barium into proximal excluded colon occurred at same rate as filling of the distal colon. Emptying time of the colon was the same as prior to surgery. Asterisk denotes percentage of barium in small intestines.

after ileocolostomy filling was found to commence between the second and fourth hours. This two-hour difference was seen in the majority of instances, the exception being a difference of less than two hours. In no case was the time of colonic filling the same as preoperatively or prolonged. The interval of time between operation and motility tests appeared to make no difference, the longest interval being four months. Ginzburg, Colp, and Sussman[2] found in the human being that a barium meal reached the stoma of an ileocolostomy between the fourth and sixth hours.

A significant observation was the consistency of retrograde filling of the proximal excluded colon (Figs. 6 and 7), which occurred uniformly

in all animals. The barium which entered at the site of anastomosis appeared to fill the proximal colon to the same extent and at the same rate as the distal colon. This has been frequently described in the human being.[2] The distal colon is evacuated first on defecation (Fig. 6), followed by a passage of the barium from the proximal into the distal colon. Retrograde filling of the cecum was quite common, although retrograde

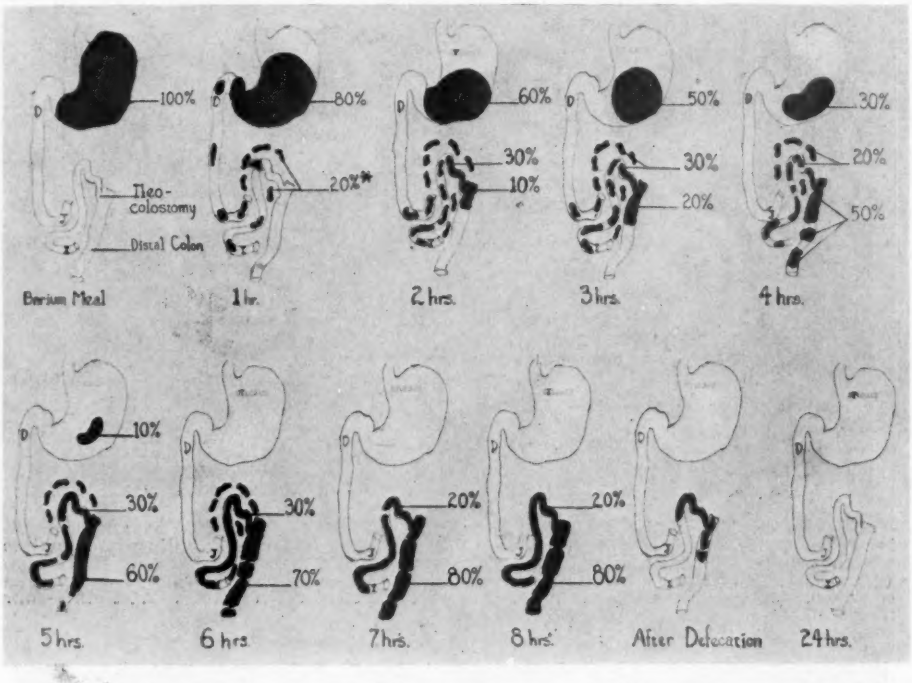

Fig. 5.—Record of average progress of motor meal in same series of dogs as represented in Figs. 3 and 4 following ileocolostomy and resection of proximal excluded colon, as drawn from fluoroscopy. Colonic filling began two and one-half to three hours earlier than in the normal control. Capacity of colon was limited so that partial evacuation of the colon occurred before the small intestine had emptied completely. The colon accommodated for limited capacity by temporary dilatation (see sixth to seventh hour record). Emptying time of the colon was the same as prior to surgery. Asterisk denotes percentage of barium in small intestine.

filling of the ileal stump was never seen. At the end of twenty-four hours the proximal excluded colon was invariably empty and the distal colon was usually empty, especially if defecation had been stimulated by feeding (Fig. 7). At no time did we observe impaction of the barium in the blind proximal colon, as reported to occur in the human being by Case.[8]

Ginzburg and his associates[2] found dilatation of the ileal loop adjacent to the anastomosis in one-third of their twenty-two patients, although evidence of ileal stasis was found in only two of them. We never observed dilatation of or stasis in the ileum adjacent to the anastomosis in the dog. This was confirmed by inspection at a subsequent operation (Fig. 8). However, we have seen temporary ileal dilatation following

partial colon resection; when the remaining colon had filled to capacity with barium, the remainder of the barium accumulated in the terminal portions of the ileum (Fig. 5) until the colon partially evacuated and could accommodate more barium. Gastric emptying time appeared to be shortened by one-half to one hour. Whether this is of significance is doubtful.

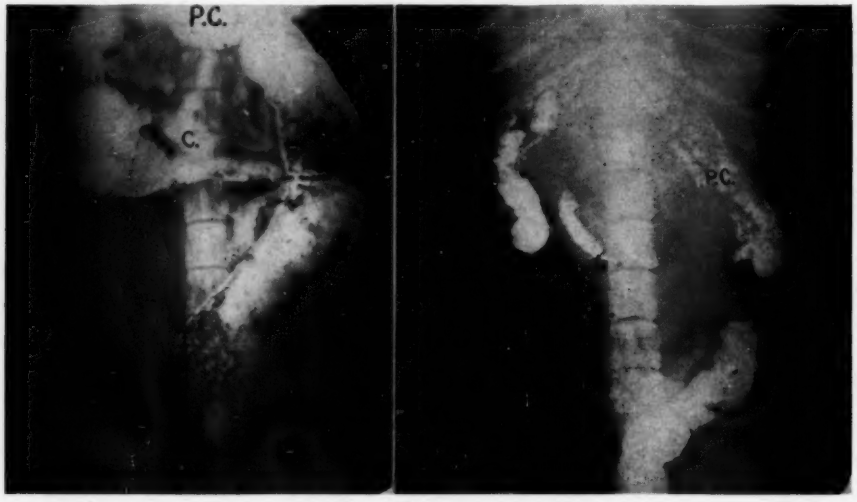

Fig. 6.—*A*. X-ray film following ileocolostomy. *XX'* marks site of anastomosis. Progress of barium meal at sixth hour. Note the degree of colonic filling at this time with retrograde filling of proximal excluded colon (*P.C.*) as far back as the cecum (*C*). *B*. Film of same animal two hours later, during which interval defecation had occurred. Note degree of emptying of proximal excluded colon (*P.C.*). At twenty-four hours entire colon had emptied.

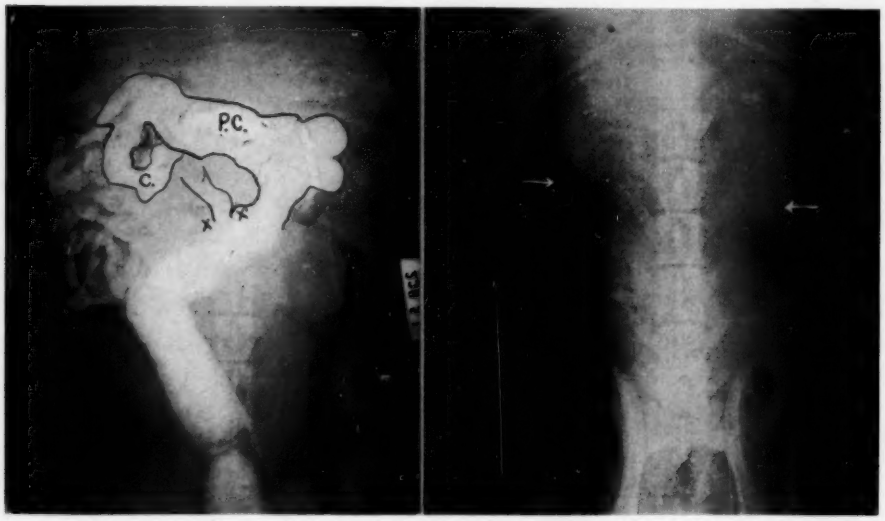

Fig. 7.—*A*. X-ray film of pregnant dog following ileocolostomy. Margins of proximal excluded colon (*P.C.*) and anastomosis (*XX'*) outlined with ink. Progress of barium at sixth hour. Note degree of colonic filling at this time with retrograde filling of proximal excluded colon (*P.C.*) as far back as the cecum (*C*). *B*. Film of same animal taken at twenty-fourth hour after defecation. Note complete evacuation of barium from all segments of the colon. Arrows point to fetuses which were delivered three weeks after the ileocolostomy.

Barium enemas usually revealed a simultaneous filling of the proximal colon and terminal ileum; whether the ileum or proximal colon filled first was variable, but the difference in time was slight. Dilatation of the terminal ileum was seen in none of the animals even with barium enema. Expulsion of the enema from all portions of the colon was usually as complete as prior to the ileocolostomy.

Fig. 8.—Photograph of ileocolostomy taken at time of resection of proximal excluded colon. Note that ileum (*I*) is of normal caliber and that colon proximal to anastomosis (*P.C.*) is of about the same dimensions as distal colon (*D.C.*).

The clinical course of these animals postoperatively was satisfactory. During a four-month course no symptoms of bowel obstruction and no diarrhea or colitis occurred. The animals' appetites were excellent, the majority of them gaining 5 pounds or more in weight (10 to 15 per cent of total body weight).

The ileocolostomy was inspected at the subsequent resection of the proximal colon (Fig. 8). The anastomosis was usually covered by loosely adherent bands of omentum, which apparently contributed to its blood supply. The ileum was of normal dimensions and color and the stoma

permitted the insertion of the tip of the index finger from the colonic side. No evidence of dilatation or obstruction was present. The proximal excluded colon was of normal caliber and appeared the same in every respect as the distal colon. On inspection of the specimens of proximal colon following resection, they were seen to contain soft, formed fecal matter. The inverted ileal stump was well healed in all specimens, its lumen empty, and regurgitation into this structure appeared unlikely.

Fig. 9.—Photograph of fresh specimen of ileocolostomy from the same dog shown in Fig. 8; anastomosis removed three months after the resection of the proximal excluded colon. Note the ample stoma of the anastomosis *XX'* which is approximately 2.8 cm. in circumference. The mucosa of the ileum (*I*) and the distal colon (*D.C.*) appeared normal.

Observations Following Partial Colon Resection.—Resection of the colon proximal to the anastomosis was undertaken as a second-stage procedure following ileocolostomy. The segment removed included the inverted ileal stump, the cecum, ascending colon, transverse colon, and the upper portion of the descending colon. This was accomplished in all

nine dogs without a single mortality. The colon was removed as close to the anastomosis as possible to decrease the amount of blind colon left behind. The colon was sectioned transversely and inverted with a row of interrupted catgut sutures as described for the anastomosis. A second row of similarly applied silk sutures inverted the colon still more. The advantage of interrupted sutures for reliable closure was striking. In previous operations on dogs we had learned that the procedure of "open" anastomoses with the dog's colon was followed by a high mortality. The animals were treated postoperatively as they were after the ileocolostomy. The postoperative course of these animals was as uneventful as after ileocolostomy. None of the animals developed diarrhea, weight was maintained, and they appeared to be in good health.

A similar series of barium progress meal studies was made in the nine dogs and Fig. 5 is a composite representation of the average progress of the barium meals in all dogs following ileocolostomy and resection of the proximal excluded colon. Colonic filling was further shortened by one-half to one hour, a total shortening of two and one-half to three hours from the normal control observations. Gastric emptying time was about the same as after ileocolostomy, but emptying of the ileum appeared to be impeded by the limited capacity of the colon (Fig. 5, *8 hrs.*). It usually required a defecation to evacuate the colon partially before the small intestine emptied completely. This appeared to have no permanent effect on the terminal ileum. The animals were capable of emptying their colons as completely after partial colon resection as before, and at the end of twenty-four hours the colon no longer contained any residual barium. Frequently we noted a compensatory dilatation of the distal colon (Fig. 5, *6 hrs.-7 hrs.*)

DISCUSSION

That retrograde filling of the proximal excluded colon should have been an invariable accompaniment of the ileocolostomy is an item of considerable practical importance. Certainly the segment of the colon proximal to the anastomosis cannot be considered to be at physiologic rest. The fact that it evacuates synchronously with the distal colon, and that it contains dehydrated fecal matter, points further to its continued activity as under normal conditions. Whatever benefits are to be described as resulting from the procedure of ileocolostomy cannot be ascribed, we feel, to diversion of the fecal stream.

That colonic filling should commence two hours earlier following ileocolostomy, and still sooner after the resection of the proximal colon, appears to be due to the lack of a physiologic sphincter. Operative findings suggested anastomotic stomas far more patulous than the ileocecal sphincter. Obviously such rapid emptying of the small intestine is undesirable and efforts should be directed toward decreasing the speed of progress of the meal out of the small intestine. Barium enemas after

ileocolostomy further showed the patulous state of the new anastomosis. It is interesting to note that one of the arguments offered in favor of an end-to-side ileocolic anastomosis over the side-to-side technique was the preservation of the circular muscle fibers of the ileum and therefore a continued sphincter action at the stoma. Our observations do not support this contention.

We must not overlook the fact that our experimental procedure differs in two important aspects from the problem in the human being. First, we are dealing with the dog's colon which is shorter, smoother, and more tubular than the human colon. Second, our proximal excluded colon is essentially a normal one, whereas in the human being it is the site of some pathologic change. Whether the diseased proximal colon would evacuate its barium as rapidly as it did in our animals is another problem.

From our observations we feel that the chance of the blind loop of colon or inverted ileal stump developing pathologic changes due to its conversion into a blind loop is unlikely, for the colon can empty in the normal direction, and regurgitation into the ileal stump does not usually occur. Furthermore, neither of these two operative procedures interfered with the state of nutrition of the animals.

CONCLUSIONS

1. Ileocolostomy in the dog was followed by a two-hour decrease in the time of colonic filling. Following resection of the colon proximal to the anastomosis, this time was still further shortened.

2. Retrograde filling of the proximal excluded colon was an invariable accompaniment of ileocolostomy in dogs.

3. The proximal excluded colon cannot be assumed to be placed at physiologic rest as a result of ileocolostomy; nor does it appear to be likely to develop any pathologic changes as a result of the procedure.

4. Resection of the proximal one-half of the colon of the dog is frequently associated with temporary compensatory dilatation of the distal colon and temporary ileal stasis, apparently due to a limited colonic capacity.

5. The procedures of ileocolostomy and partial colonic resection in the dog can be accomplished without alteration of the nutrition and health of the animal.

We are obliged to Dr. Sidney Portis for suggestions and help, to Mr. Lamar Walker for technical assistance, and to Dr. Harold Laufman for drawing Figs. 1 and 2.

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THE PATHOGENICITY OF THE BACTERIA OF APPENDICITIS PERITONITIS

An Experimental Study

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PERITONITIS secondary to acute perforated appendicitis is rarely caused by a single type of bacterium. On the contrary, the bacterial flora of the peritonitis exudate is mixed and varied, and all of the intestinal bacteria may be found in the peritoneal exudate in such cases. In a previous study at the Henry Ford Hospital in 1938,[1] sixteen species of aerobic microorganisms and at least eighteen species of anaerobes were described in the purulent exudate taken from the immediate vicinity of the perforated appendix of 100 cases. Every exudate yielded at least one type of bacterium and in no instance was an entirely negative culture obtained. Three or more species of bacteria were recovered from 96 of the 100 cases and as many as seven types were occasionally isolated, similar to the findings of Weinberg, Prevot, Davesne, and Renard in 1928.[2] The average number of anaerobic species in a case often exceeded that of the aerobic, agreeing with the previous reports of Veillon and Zuber,[3] Runeberg,[4] and Heyde.[5] Among the aerobes recovered were *Bacillus coli,* streptococci, *B. pseudodiphtheriae,* staphylococci, *B. lactis aerogenes, B. proteus, B. alkaligenes, B. subtilis,* and *B. mesentericus;* and among the anaerobes were *B. melaninogenicum,* streptococci, gram-negative diplococci, *B. thetoides, B. fragilis,* and members of the Clostridium group.

In this paper the pathogenicity of these bacteria in pure and mixed culture has been studied. The aerobic organisms were cultivated for twenty-four hours in beef extract broth or brain broth. Two cubic centimeters of this material were then injected subcutaneously and intraperitoneally into guinea pigs and the results are shown in Fig. 1. By using liquid media it was thought the results obtained would represent not only the virulence of the bacteria themselves but also the toxicity of their accumulated metabolic products. The majority of the strains tested produced minor local lesions or cellulitis about the point of subcutaneous inoculation, but usually failed to cause a fatal peritonitis. The aerobes capable of producing a fatal peritonitis included some strains of *B. coli, B. pyocyaneus,* and *B. alkaligenes.* Twenty-one strains of *B. coli* were thus tested and three of these were quite virulent, producing large areas

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of cellulitis and rapidly fatal peritonitis. The low virulence of the remaining eighteen was quite surprising. The nonhemolytic aerobic streptococcus, which usually presented the cultural characteristics of the *Streptococcus faecalis,* was found to have little or no virulence.

Fig. 1.—Results of the injection of pure cultures of bacteria subcutaneously in a guinea pig (see Table III, Case 2). *1. B. coli.* *2.* Aerobic streptococcus. *3. B. pyocyaneus.* *4. B. melaninogenicum.* *5.* Anaerobic coccus. Note the very minor lesions produced.

The virulence of these aerobic bacteria, particularly *B. coli,* for guinea pigs and rabbits could be greatly increased by the coincidental injection through a large bore needle of many particles of autoclaved sterile tissue. For example, if an avirulent culture of *B. coli* was injected along with many fine pieces of autoclaved brain or muscle tissue, cellulitis and fatal peritonitis invariably occurred. Similar observations have been made previously. Halsted,[6] working with *Staphylococcus aureus,* found that dogs did not develop peritonitis when a bouillon culture of the bacterium was introduced into the peritoneal cavity. However, if a small piece of potato was introduced along with the bacteria, a fatal peritonitis de-

veloped. Similarly, if a small piece of omentum was tied off and strangulated within the abdominal cavity, its contamination with staphylococci frequently resulted in peritonitis.

Many of the anaerobic organisms were difficult to cultivate in pure culture. By using deep tubes containing brain broth and a small amount of blood, a fairly good growth was usually obtained under strict anaerobic conditions. In the case of the anaerobes, 2 c.c. of a forty-eight- or seventy-two-hour culture were usually used for the inoculations. The

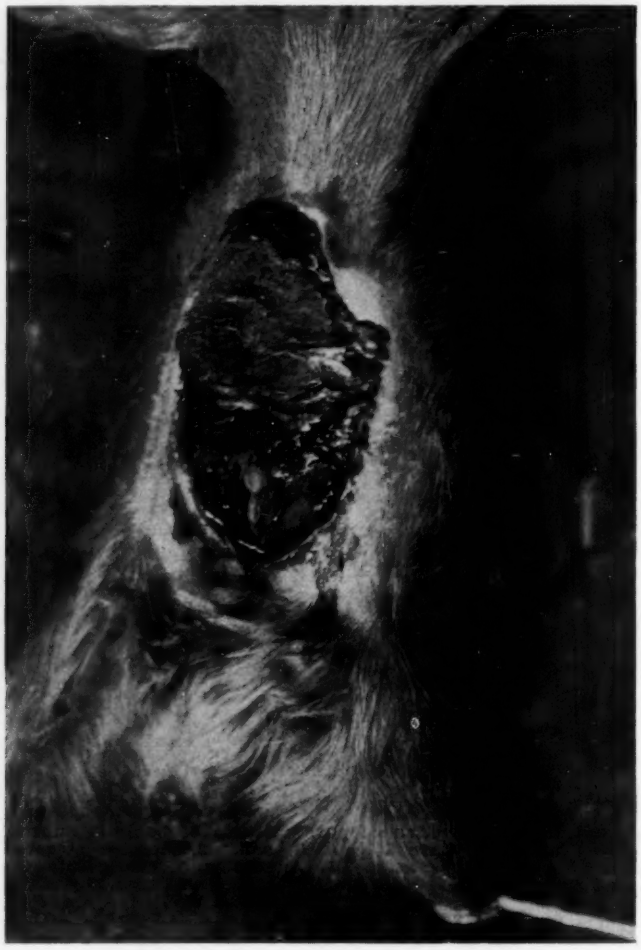

Fig. 2.—Extensive cellulitis and gangrene produced by the subcutaneous inoculation of a mixed culture of the same bacteria used in Fig. 1: *B. coli*, aerobic streptococcus, *B. pyocyaneus*, *B. melaninogenicum*, and anaerobic coccus (see Table III, Case 2).

majority of the anaerobic bacteria investigated did not produce a fatal peritonitis, with the exception of hemolytic streptococci, *B. thetoides*, and *B. fragilis*. The anaerobic *B. melaninogenicum* frequently found in our series of peritonitis exudates was separated with great difficulty from a nonhemolytic streptococcus with which it was frequently and intimately associated. Both were found to be relatively nonpathogenic.

A study of Tables I and II shows that the majority of bacteria found in appendicitis peritonitis, when injected in pure culture, did not produce a fatal peritonitis. If, however, several or more strains of these bacteria found in a given case of peritonitis were mixed and cultivated simulating their existence in the peritonitis exudate, their composite virulence was greatly increased. The synergistic effect produced by these bacteria was repeatedly demonstrated. The various strains of bacteria

Fig. 3.—Cutaneous gangrene in the guinea pig produced by the subcutaneous injection of a mixed culture of *B. coli*, nonhemolytic streptococcus, anaerobic coccobacillus, anaerobic coccus (large), and anaerobic micrococcus (see Table III, Case 1).

isolated from a given case of appendicitis peritonitis were inoculated in pure culture subcutaneously and intraperitoneally into laboratory animals and their effect noted. Subcutaneously, relatively minor lesions usually were the result. (Table III and Fig. 1.) Intraperitoneally the great majority of these bacteria did not produce a fatal peritonitis in the dosages employed. When the same strains of organisms were mixed, cultivated, and then injected into similar experimental animals, it was

TABLE I

PATHOGENICITY OF AEROBIC BACTERIA IN PURE CULTURE FOR GUINEA PIGS

AEROBIC BACTERIA	NO. OF STRAINS	SUBCUTANEOUS INOCULATION	INTRAPERITONEAL INJECTION
1. *B. coli*	18	Negative; slight local reaction; cellulitis	Survived
	3	which may produce cutaneous gangrene	Fatal peritonitis
2. Streptococcus, nonhemolytic	9	Negative, or small area of induration	Survived
3. *B. pseudodiphtheriae*	3	Small area of cellulitis	Survived
4. Streptococcus, green producing	2	Cellulitis with small area of central gangrene; localized abscess with surrounding area of cellulitis	Listless, survived
5. Streptococcus, hemolytic	2		Survived
6. *B. pyocyaneus*	3	Diffuse cellulitis	Dead in less than 20 hr.
7. *Staph. aureus*	2	Localized abscess	Survived
8. *B. lactis aerogenes*	2	Localized induration	Survived
9. *B. proteus*	2	Negative, or local induration	Survived
10. *B. alkaligenes*	2	Negative	Animals dead in 36-48 hr.
11. *B. subtilis*	2	Negative	Survived
12. *B. mesentericus*	2	Negative	Survived

TABLE II

PATHOGENICITY OF ANAEROBIC BACTERIA IN PURE CULTURE FOR GUINEA PIGS

ANAEROBIC BACTERIA	NO. OF STRAINS	SUBCUTANEOUS (2 C.C.)	INTRAPERITONEAL (2 C.C.)
1. *B. melaninogenicum*	3	Induration with small crepitant abscess in some instances	Survived
2. Streptococci, nonhemolytic	4	Negative; local induration; local abscess	Survived
	5		Survived
	3		
3. Streptococci, hemolytic	2	Local abscess	Death in 24 hr.
4. *B. thetoides*	2	Cellulitis with death of animals	Death in 24 hr.
5. *Staphylococcus*	2	Local abscess	Survived
6. *B. fragilis*	1	Local abscess followed by death	Death in 72 hr.
7. *Streptobacterium*	1	Local abscess	Death in 24 hr.
8. *B. pseudodiphtheriae*	3	Negative	Survived
9. *Cl. aerofoetidum*	1	Cellulitis, animals survived	Survived
10. *Cl. sporogenes*	1	Local inflammation	Survived
11. *Cl. fallax*	1	Crepitant cellulitis	Survived
12. Gram + streptobacillus	1	Negative	Survived
13. *Cl. welchii*	2	Cellulitis, ulceration, and gangrene	Survived

found that an equal or smaller dose resulted in extensive areas of cellulitis frequently accompanied by gangrene (Figs. 2, 3, and 4; Table III) and frequently overwhelmingly fatal peritonitis.

These facts combined with the observation that many of these bacteria grow sparsely in pure culture, but profusely in mixed culture, suggest that they exist in the peritonitis exudates in a state of symbiosis and that their synergistic effect plays a large part in the infection.

Fig. 4.—Gangrene following subcutaneous injection of mixed culture of *B. lactis aerogenes*, *B. pseudodiphtheriae*, nonhemolytic streptococcus, *B. melaninogenicum*, anaerobic micrococcus, and *Cl. aerofoetidum* (see Table III, Case 5).

DISCUSSION

There are many reasons why it is difficult to estimate the human pathogenic power of the bacteria associated with appendicitis peritonitis. Not only are there many different species of bacteria found in the peritonitis exudate, but considerable variation in virulence also occurs among different strains of the same species. Many of the bacteria probably lose their pathogenic power under the repeated sub-

TABLE III

	BACTERIA ISOLATED	PATHOGENICITY IN PURE CULTURES FOR GUINEA PIGS		PATHOGENICITY IN MIXED CULTURES FOR GUINEA PIGS	
		SUBCUTANEOUS (2 C.C.)	INTRAPERITONEAL (2 C.C.)	SUBCUTANEOUS (2 C.C.)	INTRAPERITONEAL (2 C.C.)
Case 1.	*B. coli*	Negative	Survived	Extensive cellulitis in center of which gangrene usually occurred	Animals dead in 18-36 hr.
	Nonhemolytic streptococcus (aerobic)	Negative	Survived		
	Gram + cocobacillus (anaerobic)	Local induration	Survived		
	Anaerobic coccus	Local abscess	Survived		
	Anaerobic microstreptococcus	Local induration	Survived		
Case 2.	*B. coli*	Negative	Survived	Extensive cellulitis with gangrene	Animals dead in 12-24 hr.
	Nonhemolytic streptococcus	Negative	Survived		
	B. pyocyaneus	Cellulitis	Death in 48 hr.		
	B. melaninogenicum	Local abscess	Survived		
	Anaerobiccoccus	Slight induration	Survived		
Case 3.	*B. coli*	Negative	Survived	Cellulitis with central abscess formation and ulceration; animals survived	Animals dead in 5-8 days
	Staph. aureus	Local abscess	Animals dead in 14 days		
	B. melaninogenicum	Local induration	Survived		
	Anaerobic streptococcus	Local induration	Survived		
Case 4.	*B. coli*	Local cellulitis	Survived	Extensive hemorrhagic cellulitis with death of animals in 48-72 hr.	Animals dead in 24-48 hr.
	Nonhemolytic streptococcus (aerobic)	Negative	Survived		
	B. melaninogenicum	Induration with small abscess	Survived		
	Anaerobic micrococcus	Induration with small abscess	Survived		
	B. fragilis	Local abscesses; death in 4 days	Death in 72 hr.		
Case 5.	*B. lactis aerogenes*	Slight induration	Survived	Extensive cellulitis with gangrene and ulceration; animals survived	Animals dead in less than 24 hr.
	B. pseudodiphtheriae	Negative	Survived		
	Nonhemolytic streptococcus	Slight induration	Survived		
	B. melaninogenicum	Local induration	Survived		
	Anaerobic micrococcus	Negative	Survived		
	Cl. aerofoetidum	Cellulitis	Survived		
Case 6.	*B. coli*	Small abscess	Survived	Large area of cellulitis with central gangrenous slough and ulceration	Animals survived
	B. pseudodiphtheriae	Large area of cellulitis	Survived		
	Nonhemolytic streptococcus	Slight induration	Survived		
	B. pyocyaneus	Large area of cellulitis with small area of gangrene	Survived		
	Staph. albus hemolyticus	Slight induration	Survived		

cultivations necessary for their isolation in pure culture and their proper identification, and this may have occurred in our experiments. The laboratory animals used to test virulence may have a susceptibility entirely different from the human being and may actually possess either a natural individual or species immunity. Evidence is accumulating that some bacteria such as the anaerobic streptococci are definitely pathogenic for human beings under certain conditions, yet all attempts to demonstrate their pathogenicity in experimental animals have failed. Finally, metabolic diseases, individual human variations in general health, and susceptibility to infection are all factors of importance which determine the pathogenic power of bacteria in an individual case.

In the experiments presented in this paper there is strong evidence that the accumulative action of all the bacteria, aerobic and anaerobic, determine to a large extent the nature and severity of the peritoneal infection. It appears that slightly or apparently nonpathogenic microorganisms may play an important part in the course of the peritonitis by increasing the virulence of the bacteria with which they are associated.

Symbiosis in disease has attracted relatively little attention in medicine and surgery. The course of medical investigation and reasoning since the time of Pasteur, and more particularly Koch, has been toward the monoetiology of disease. Indeed, the fulfillment of Koch's postulates is generally required for the establishment of the etiology of a disease. Largely for this reason the true nature of many pathologic processes has remained obscure.

The biologic relations of microorganisms are of the greatest significance in the economy of nature and in the production of disease (Kendall[7]). Bacteria in nature do not grow in pure culture, although in the tissues of man or animals they may do so as disease-producing bacteria. One of the important functions of bacteria is to reduce dead organic matter into mineralized salts, the successive steps being effected by different species of microbes. Frequently the products of such symbiotic activity are greater than the total of the separate activities of the bacteria. In man and animals, natural infection with more than one bacterium is relatively frequent, and the particular combinations which may occur to a large extent determine the course of the disease. Rogers[8] (1889) was the first to show that *B. prodigiosus* added to the bacillus of malignant edema made sublethal injections of this anaerobe fatal for rabbits. Novy[8] found association of *B. proteus* and *B. oedematiens* produced rapid death of guinea pigs. Barrien[8] (1920) noted that *B. proteus* and nonpathogenic spore-bearing aerobes in wounds exhibited the virulence of pathogenic bacteria. Kammerer[9] introduced the term "synergism" into bacteriologic nomenclature to indicate the sum activity of two or more microorganisms. He cited examples of synergistic action in observations on the reduction of pure bilirubin and mesobilirubin to urobilin by emulsions of human feces. The syner-

gistic activity of *B. putrificus* and certain aerobes he believed was responsible for this. Roux and Yersin[8] restored the virulence of an avirulent strain of *B. diphtheriae* by the addition of a nonfatal dose of the streptococcus of erysipelas. Jacobson,[13] Wolf,[10] Albert and Kilman,[11] Roos,[12] and Hudson[13] all found that the virulence of *B. influenzae* was increased when mixed with streptococci. Coley[14] showed the streptococcus was more virulent in combination with the *B. prodigiosus.* Jennings[15] (1923) discussed the role of *Cl. welchii* in appendicitis, and he believed that *Cl. welchii* infection occurred as a rule in symbiosis with a number of other bacteria.

Weinberg, Prevot, Davesne, and Renard (1928)[2] found anaerobes predominant in purulent exudates of gangrenous appendicitis. Their experiments suggested the possibility that not only appendicitis but also peritonitis was the result of the combined action of bacterial mixtures.

Meleney, Olpp, Harvey, and Jenn[16] (1932) observed that if more than one type of intestinal bacterium was present in the peritoneal exudate, the clinical course of the illness was much more serious than when only one was present. They studied the pathogenicity of *B. coli,* nonhemolytic streptococci, and *Cl. welchii* which were the organisms commonly found by them in peritonitis. All four possible combinations of these three species were made. When any two or all three types were combined, the mixture was lethal in quantities considerably less than the lethal doses in pure culture. This work clearly shows the synergistic activity of these three symbionts in peritonitis. In our experiments a similar cumulative action of many more species of bacteria, both aerobic and anaerobic, in peritonitis has been shown.

The symbiotic existence of the intestinal bacteria within the intestinal tract is generally recognized. Experimental evidence indicates that the same bacteria exist in a similar state in the peritonitic exudates of perforated appendicitis. The synergistic pathogenic effect of the different strains of bacteria growing in symbiosis has been demonstrated by our experiments. These experiments also substantiate our previous observation[1] that the more clinically severe cases of appendicitis peritonitis occurred most frequently when five or more species of bacteria were present in the exudate. No case died in which only one species of bacterium was found.

As noted previously the low virulence of the majority of strains of *B. coli* isolated by us was unexpected and surprising. Jordon[17] regarded the pathogenicity assigned to *B. coli* by some investigators, notable French bacteriologists, to be greatly exaggerated. He regarded the frequent ascription of various inflammatory processes, particularly those occurring in the appendix and peritoneum, to the unaided activities of *B. coli* to be without sufficient justification. Benians[18] was able to inject intraperitoneally 2500 million living *B. coli* from a twenty-four-hour culture in saline suspensions into rabbits with no obvious ill

effects, nor any abnormality in the peritoneal cavity beyond slight injection. However, by adding gum tragacanth to the *B. coli* suspensions, he was able to produce death by intraperitoneal injection in rabbits within thirteen to thirty-six hours. Steinberg[19] cited the frequent inability of investigators to produce a fatal peritonitis experimentally by intraperitoneal injections of saline suspensions of *B. coli*, and he adopted the method of Benians of inoculating *B. coli* suspended in gum tragacanth.

In summary, an analysis of the literature and of our experiments indicates that appendicitis peritonitis is usually a "polymicrobic" infection caused by the synergistic pathogenic action of a group of bacteria existing in the peritonitis exudate in a state of symbiosis. Correlation of clinical and experimental studies shows that the greater the number of bacterial species present within the exudate, the greater the severity of the peritoneal infection is likely to be.

CONCLUSIONS

1. The pathogenicity of the aerobic and anaerobic bacteria most frequently isolated from the peritoneal exudate of 100 cases of acute perforated appendicitis was studied in experimental animals.

2. The great majority of these bacteria did not produce a fatal peritonitis when injected in pure culture.

3. The ascription of acute perforated appendicitis peritonitis to the unaided activity of *B. coli* or other single strains of bacteria seems without sufficient justification in the average case.

4. Many avirulent strains of bacteria, particularly *B. coli*, become highly virulent in the presence of dead sterile tissue within the peritoneal cavity.

5. In mixed culture these bacteria show a synergistic action producing a high degree of pathogenicity.

6. Acute perforated appendicitis peritonitis appears to be an infection resulting from the synergistic activities of the various bacterial symbionts present in a given case.

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PEPTIC ULCER IN MECKEL'S DIVERTICULUM CAUSING INTRINSIC INTESTINAL OBSTRUCTION

Report of Two Cases

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MECKEL'S diverticulum is a congenital anomaly which occurs in about 1 to 2 per cent of all persons. The mucous membrane of the diverticulum usually is of the ileal type, but may be gastric and, less often, duodenal, jejunal, pancreatic, or colonic. Schaetz[1] found gastric mucosa in 16 per cent of his specimens, Carlson[2] and Bussey[3] in 15 per cent of specimens removed surgically at the Mayo Clinic. Hudson and Koplik[4] found that 52 per cent of their specimens, which were the sites of acute lesions, contained gastric mucosa. This may indicate that the presence of gastric mucosa is more likely to be associated with pathologic change than is the presence of ileal mucosa.

Halstead[5] in 1902 reviewed 69 cases of intestinal obstruction secondary to Meckel's diverticulum, and Deetz[6] in 1907 reported on an acute perforation at the base of a Meckel's diverticulum in a boy 9 years old. The clinical picture of peptic ulceration of Meckel's diverticulum, however, is relatively new. Cobb,[7] in 1936, analyzed 100 cases of probable peptic ulcer in Meckel's diverticulum, most of which had been reported in the literature since 1924. In 66 cases gastric mucosa was found in the diverticulum on microscopic examination. In the remaining cases it either was not found or was not mentioned. Seventy-four per cent of the patients were 15 years of age or less. Eighty-one ulcers afflicted men, 14 afflicted women, and in 5 instances the sex of the patients was not stated. The ratio of the incidence of Meckel's diverticulum among men to that among women was 2:1. Eighty per cent of the patients had abdominal pain of some type. The most frequent complication, bleeding from the rectum, occurred in 72 per cent of the cases. Perforation was found in 55 per cent of the cases, either at the time of operation or on post-mortem examination.

Two features repeatedly mentioned by most investigators of the subject under consideration is that the lesion is situated in the region of ordinary intestinal mucosa close to the boundary of the heterotopic gastric mucosa of fundic type and that, usually, a single ulcer is present. When the entire pouch of the diverticulum is lined with gastric mucosa, the ulcer is situated in the ileum close to the neck of the Meckel's

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diverticulum. The macroscopic and microscopic pictures resemble those of typical, chronic gastric and duodenal ulcers.

Analysis of secretion of the heterotopic gastric mucous membrane obtained from an open umbilical fistula by Tillmanns, Lexer, Denucé, Rosthorn, Stone, and A. L. Taylor[8] proved that it contained both pepsin and hydrochloric acid. Lindau and Wulff[9] expressed the belief that the occurrence of ulcers in Meckel's diverticulum lends support to the theory of the biochemical origin of peptic ulcer.

As previously stated, most of these ulcers produced either bleeding or some type of abdominal pain, with or without symptoms and signs of peritonitis caused by perforation. In the cases which are to be presented herein the scarring of the chronic peptic ulcers had, however, so narrowed the ileum that partial obstruction had occurred, and we believe it was this partial obstruction which was causing the recurrent abdominal pain associated with vomiting in the first case and the colicky pain in the second.

On the basis of study of the cases reported by Halstead and Cobb and a review of the cases which have appeared in the literature, we have been unable to find any instance in which a peptic ulcer in a Meckel's diverticulum caused scarring and resultant intrinsic partial or complete intestinal obstruction. Reported cases in which the condition has been associated with intestinal obstruction have shown that such obstruction was of the extrinsic type. Brown and Pemberton[10] reported 2 cases in which an ileac ulcer was situated at the mouth of a Meckel's diverticulum. In both cases gross and occult blood was found in the stools and in both there were annular lesions causing obstruction which apparently were similar to the lesion in our cases. Brown and Pemberton thought the Meckel's diverticula in their 2 cases were incidental and chose to call the ulcers "solitary ulcer of the ileum" because the Meckel's diverticula contained ileac mucosa and because there was no evidence of gastric mucosa. Cobb, as well as Brown and Pemberton, has called attention to the presence of an ulcer in or near a Meckel's diverticulum in which no gastric mucosa was demonstrable, and also to the absence of such ulceration in certain cases in which gastric mucosa was present. The former condition is difficult to explain, but the latter is no more so than is the explanation of the absence of peptic ulcer in the duodenum of most persons.

REPORT OF CASES

CASE 1.—The patient, a married woman, 22 years old, registered at the Mayo Clinic on Sept. 4, 1938, complaining of abdominal cramps of ten years' duration. In 1928, at the age of 12 years, she had had occasional attacks of cramplike pain across the lower part of the abdomen, which extended into both lumbar regions, and she stated that the left leg became stiff with each attack. Sometimes these attacks were associated with nausea and vomiting. In 1933, in the course of an exploratory operation performed elsewhere, the appendix had been removed, but the patient was told that the appendix was not the cause of her condition.

In 1935 attacks had occurred about once a month; fecal vomiting had been associated with one attack. These attacks had persisted, and in 1937 another exploratory operation had been performed, but nothing abnormal had been found.

The patient had consulted many physicians. Her condition had been diagnosed as "colitis," "adhesions" and "functional colon." The disability had progressed, however, so that at the time of the patient's admission to the Clinic she was experiencing almost constant abdominal pain which could be relieved only by the hypodermic injection of morphine sulfate. For many years she had taken laxative agents frequently to relieve constipation. There was no history of bloody or tarry stools. Menses, which had begun when the patient was 13 years of age, had been regular until June, 1938, and since that time had been eight to ten days late.

On physical examination at the clinic the patient appeared to be constitutionally inferior. The abdomen was not distended, but pelvic examination revealed that the left Fallopian tube and ovary were slightly enlarged and tender.

Results of routine laboratory examinations, consisting of urinalysis, leucocyte counts, determination of sedimentation rate and of blood urea, study of smears of the blood and a flocculation test, were normal or within the range of normal. The value for hemoglobin was 10 Gm. per 100 c.c. of blood; erythrocytes numbered 4,040,000 per cubic millimeter; and roentgenograms of the thorax revealed nothing abnormal.

An exploratory operation was advised, but no assurance of relief was given. Accordingly, on Sept. 7, 1938, the abdomen was opened by one of us (J. M. W.) through a low midline incision. A hydrosalpinx of the left tube was found and left salpingectomy was performed. This lesion was not felt to be the source of the trouble, however. On further exploration a Meckel's diverticulum was found about 60 cm. (2 feet) from the ileocecal valve, which measured 5 cm. in diameter and was greatly thickened and hypertrophied. The lumen of the small intestine above the diverticulum was dilated to about two times normal size and the wall was thickened and hypertrophied. Below the diverticulum the small intestine was collapsed. At the junction of the distal portion of the ileum with the diverticulum a chronic penetrating type of ulcer was encountered. The lumen of the intestine at this point would not admit the tip of the gloved fifth finger. The diverticulum and the adjacent portion of the small bowel were removed. Intestinal continuity was re-established by closure of both ends and the making of a side-to-side anastomosis. A Witzel type of enterostomy was performed above the anastomosis as a safety measure. The enterostomy tube was brought to the outside through a stab wound in the right lower quadrant of the abdomen.

The patient made an uneventful convalescence, except for the development of a small abscess in the abdominal wall. This subsided after incision and drainage. The enterostomy tube was removed on the sixteenth postoperative day and the patient was dismissed from the Clinic on Oct. 12, 1938, about a month after operation. At this time she was free from all pain and a recent communication revealed that she had had no recurrence of the symptoms which she had experienced prior to operation.

The pathologist who studied the specimen removed at operation reported that a chronic penetrating type of ulcer was situated at the junction of the distal portion of ileac mucosa with the Meckel's diverticulum, and that heterotopic gastric mucosa was present in the diverticulum (Fig. 1 *a* and *b*). The heterotopic gastric mucosa was of the fundic type and contained many parietal, acid-secreting cells.

CASE 2.—The patient was a man 48 years old who was first seen at the Clinic in 1924, at which time he had a rather characteristic history. Roentgenologic evidence of a duodenal ulcer with considerable deformity of the duodenum had been noted. Following medical treatment he had responded satisfactorily and had remained in good health until two months before the admission which primarily con-

cerns this report. The second admission of this patient to the clinic was on Sept. 29, 1936. For two months before his admission he had been experiencing lower abdominal colicky pains which seemed to have some tendency to be more severe in the right lower abdominal quadrant. Some degree of anorexia and much gaseous indigestion which was relieved by alkalies had been present. Twenty-four hours before admission the pains had been severe enough to necessitate the patient's sitting up in a chair all night, and he had obtained some relief after an enema.

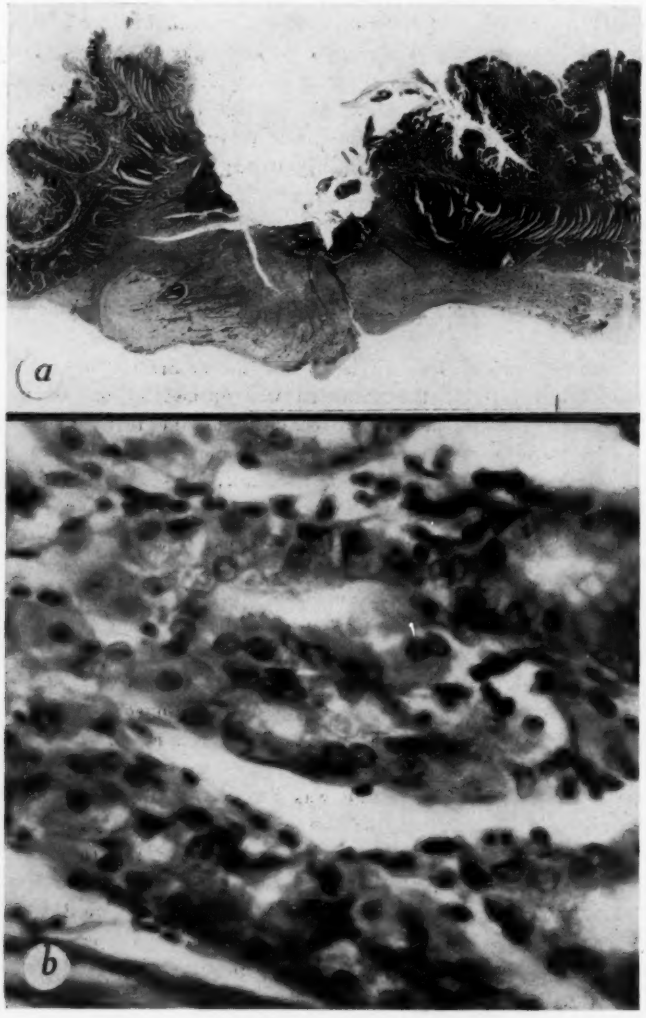

Fig. 1.—*a*. Penetrating ulcer at the junction of the distal portion of the ileac mucosa and diverticulum (hematoxylin and eosin, ×2½). *b*. Atrophic gastric mucosa, fundic type (hematoxylin and eosin, ×450).

At the time of the patient's admission to the hospital there was clinical and physical evidence of subacute intestinal obstruction. Results of complete examination of the blood, including erythrocyte and leucocyte counts, and determinations of hemoglobin, urea, chlorides, and carbon-dioxide combining power, all were negative. Results of roentgenologic examination of the thorax were negative. A plain roentgenogram of the abdomen revealed considerable dilatation of the left half of the transverse and descending portions of the colon, although a roentgenogram of the colon disclosed nothing abnormal. Roentgenologic examination made after the

patient had taken a barium meal showed the presence of an obstructing lesion within approximately 30 inches (76 cm.) of the ileocecal valve. It was visualized on the right side at about the level of the fourth lumbar vertebra. In view of these observations a diagnosis of subacute intestinal obstruction was made, with the possibility in mind that a malignant process might involve the lower portion of the ileum.

On Oct. 9, one week after admission, this patient underwent surgical exploration for the obstructing lesion in the lower part of the ileum. The operation was performed by Dr. J. deJ. Pemberton of the surgical staff. A lesion was found in the

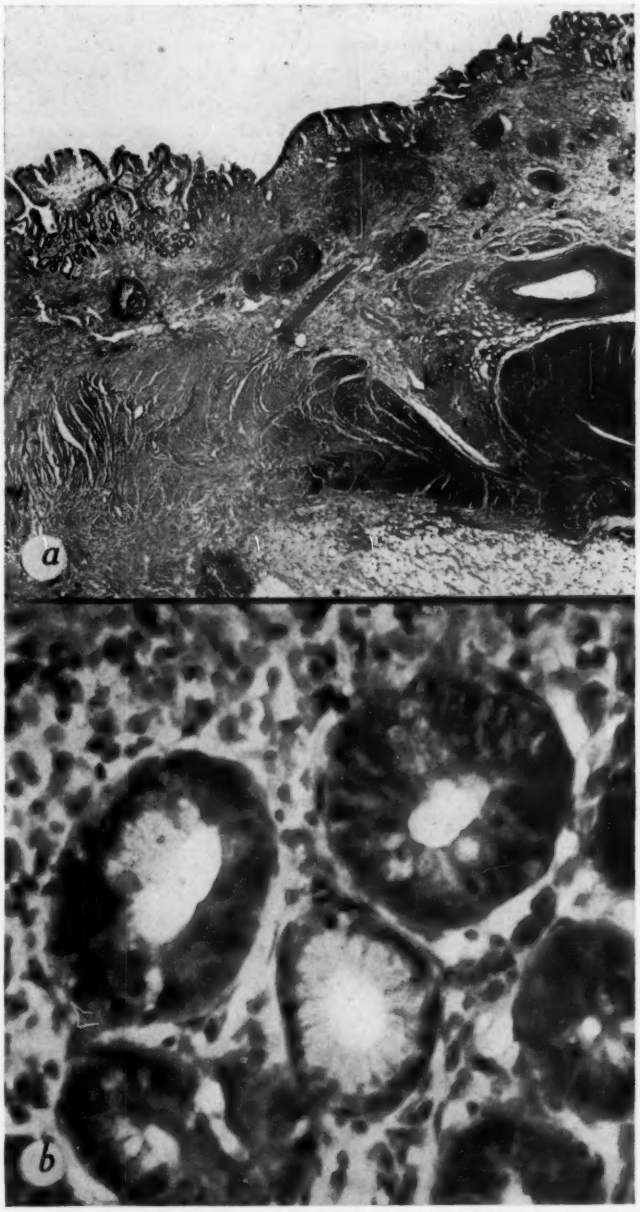

Fig. 2.—*a*. Section through ulcerating portion of lesion (hematoxylin and eosin, ×11). *b*. Glandular tissue lining diverticulum. Note typical gastric type of glands with parietal cells (hematoxylin and eosin, ×325).

lower portion of the ileum which was producing rather marked obstruction. Huge dilatation of that part of the bowel proximal to the lesion was observed. It was not possible definitely to identify the character of the obstructive process, but it seemed to be a narrow tumor somewhat similar in shape to a napkin ring, involving the ileum with an extensive inflammatory reaction in the tissue around it. Lateral anastomosis was done; no attempt was made to remove the lesion. The patient made an uneventful convalescence, and on Nov. 3 a secondary operation was performed and further surgical exploration was carried out. Arising from the bowel at a point distal to the site of the previous anastomosis at right angles was a Meckel's diverticulum which was about 1½ inches (about 3.5 cm.) in diameter and 3 inches (about 8 cm.) long. The Meckel's diverticulum was adherent posteriorly to the bowel. It contained an ulcerating lesion and was producing obstruction. The diverticulum was removed, and the stump was turned in with three rows of chromic catgut sutures and one row of silk sutures. The patient made an uneventful recovery and has remained in excellent health to the time of this report.

Microscopic examination of tissue from the ulcerating lesion as shown in Fig. 2*a* and examination of the glandular elements contained in the mucosa which lined the diverticulum in the region of the ulcer showed typical gastric-type glands which contained many parietal cells (Fig. 2*b*). Rather marked associated diverticulitis and peridiverticulitis had been present.

COMMENT

In both of these cases it would appear, after careful gross and microscopic examination of the specimens removed at operation, that intrinsic intestinal obstruction had developed in the ileum as a result of the inflammatory reaction associated with active ulceration, similar to that of peptic ulcers, in or near a Meckel's diverticulum which was found to contain gastric mucosa with typical parietal cells. This type of obstruction, since it is of an intrinsic nature, is similar to that occurring in the duodenum secondary to peptic ulceration. This type of obstruction is distinct from that usually associated with a complicated Meckel's diverticulum, which is of an extrinsic or mechanical nature and which results from the formation of adhesions and inflammatory exudate about a Meckel's diverticulum which has perforated, with the subsequent occurrence of peritonitis.

Halstead in 1902 carefully analyzed and classified the types of intestinal obstruction which result from Meckel's diverticulum, but in the 69 cases of such obstruction he collected from the literature, he found none of an intrinsic nature. Not until some time after his report was it appreciated that frequently the ulcers occasionally present in Meckel's diverticula are similar to peptic ulcers. Although none of the cases which formed the basis of Halstead's report were similar to the 2 we have presented, he included in his classification a group which would include intrinsic intestinal obstruction caused by peptic ulcer in a Meckel's diverticulum, although he did not mention the complication of peptic ulcer. "Chronic inflammation of the diverticulum and of the adjacent portion of the intestine, with cicatricial narrowing of the gut just above the diverticulum, can be the cause of obstruction. This may happen in free and in attached diverticula. The diverticulum becomes

filled with fecal matter or concretions, and the resulting inflammation extends to the intestine, ulceration and cicatrization follow, and obstruction finally develops.''

The fact that peptic ulceration in or near a Meckel's diverticulum may result in hemorrhage, penetration, or perforation with secondary extrinsic obstruction has been observed not infrequently in recent years. We believe that the 2 cases reported herein are the first reported in which proved peptic ulcer in Meckel's diverticulum resulted in intrinsic intestinal obstruction.

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CHYLOTHORAX AND CHYLOPERITONEUM

Effects of Reintroduction of Aspirated Chyle

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APPROXIMATELY 50 cases of traumatic and 100 cases of nontraumatic chylothorax have been reported in the literature. No attempt will be made to review these reports. The nontraumatic ones were reviewed very adequately by Yater[1] in 1935. We are in the peculiar position in the present report in not knowing whether the chylothorax and chyloperitoneum were traumatic or nontraumatic in origin. The history of injury suggests trauma as the etiological agent, but the findings are indicative of a nontraumatic basis. The case is reported not because of the rarity of the condition but because of the bizarre associated findings, because the effects of reintroducing intravenously some of the aspirated chyle were determined, and because many chemical studies of interest were carried out. No previous patient has been given such large quantities of chyle. Bauersfeld[2] reported the effects of the intravenous injection of 1,200 c.c. of chyle.

CLINICAL COURSE OF PATIENT

E. G., a married white female, 17 years of age, was admitted to the Vanderbilt Hospital on Dec. 3, 1939. The patient stated that she was in good health until two and one-half months prior to admission when in an automobile accident she was thrown clear of the car. She was able to walk after the accident, but a few minutes subsequently pain was experienced in the left shoulder and left supraclavicular region. Respiratory and shoulder movements were without influence on the pain. This pain subsided after about four days. It should be stated at this time that the husband of the patient was of the opinion that there had been a moderate increase in the size of her abdomen prior to the accident.

Two weeks following her injury, the patient had an attack of tonsillitis which subsided in a few days. There were no further complaints for the next two weeks, at the end of which time a tender swelling about the size of a hen's egg appeared in the left supraclavicular region. This swelling persisted for a week. Five weeks prior to admission, she noticed that she was breathing faster and that deep inspiration was more difficult. A moderate amount of pain in the chest and left supraclavicular region was experienced. Three weeks before admission, or seven weeks following the accident, it was noted that the abdomen was increasing in size and the patient complained of a feeling of fullness and of dyspnea. Her family physician was consulted and 1,500 c.c. of milky fluid were removed from the left pleural cavity. Thoracentesis was repeated on three other occasions prior to admission, and each aspiration resulted in a diminution in her dyspnea and discomfort.

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Examination on Dec. 3, 1939, showed the patient to be well developed and fairly well nourished, although there was slight wasting of the extremities. The weight of the patient was 150 pounds and she stated that this was 10 pounds greater than her average. There were no scars or abnormal masses in the neck. Respiratory excursions of the left chest were diminished and the findings on palpation and percussion indicated the presence of a great deal of fluid in the left pleural cavity. No abnormalities of the right side of the chest were noted. There was marked abdominal distention and signs indicative of much free fluid were elicited. There were no palpable abdominal masses, no tenderness, and no muscular rigidity. Pelvic and rectal examinations were negative. In the lower dorsal, sacral, and lumbar regions, there was moderate pitting edema which was probably due to the extravasation of chyle at the site of one of the pleural taps. The temperature was normal, the white blood cell count was 5,800, and the urine and stools showed no abnormality. The specific gravity of the urine was 1.026. The supravital differential count of the blood revealed 70.5 per cent polymorphonuclears, 16.5 per cent lymphocytes, and 13 per cent monocytes. The venous pressure was 225 mm. water by the Lyons-Kennedy-Burwell[3] technique. This is a moderate but not necessarily a significant elevation. Fluoroscopic and x-ray examinations of the heart, lungs, ribs, spine, clavicles, and the gastrointestinal tract showed no abnormalities except for the presence of fluid in the peritoneal and left pleural cavities.

Milky fluid was aspirated from both the left pleural cavity and the peritoneal cavity, and analyses, which will be considered subsequently, showed it to be chyle. Therapy consisted in the main of placing the patient on a fat-free diet, of aspirating frequently part of the chyle from the pleural and peritoneal cavities, and of introducing intravenously part of that which was obtained from the pleural cavity. This latter procedure was performed by the use of a closed system, consisting of two needles, rubber tubing, a three-way stopcock and a syringe, the chyle being aspirated from the chest and then immediately injected intravenously. Usually the patient had chilly sensations with vague feelings of discomfort following the introduction of chyle, but there were no severe reactions.

From Dec. 3 to Feb. 8, approximately nine weeks, the patient was on a fat-free diet which, by calculation, contained less than 5 Gm. of fat per day. During the succeeding week, she was on a low-fat diet which contained approximately 40 Gm. of fat per day. During this period of ten weeks, 29,730 c.c. of chyle were removed from the peritoneal cavity, 16,060 c.c. of chyle removed from the left pleural cavity and 11,385 c.c. removed from the chest were injected intravenously. While the patient was on a fat-free or a low-fat diet, there was a marked decrease in the total lipid concentration of the chylous fluid. The diet, however, did not cause a cessation of the accumulation of fluid, and after Feb. 15, the patient received the usual hospital diet calculated to yield 3,000 calories. This alteration in the diet resulted in a sharp and marked increase in the total lipid concentration of the fluid.

It was decided that an exploration of the thoracic duct was indicated and this was performed on Feb. 28, 1940. An incision was made in the left supraclavicular region. In the region of the junction of the internal jugular and subclavian veins, there were several large lymph vessels which contained chyle and the lymph nodes were large, soft, and white in color. No injury to the lymph channels was demonstrated. Several of the lymph channels were partially thrombosed. The internal jugular vein was a thick cord, the lumen being entirely occluded by a thrombus. The subclavian vein was not opened, but its walls appeared to be thickened. Before having determined that venous thrombosis was present, several of the dilated lymph ducts were ligated. The incision was closed without drainage.

Four days following the operation, the patient complained of numbness and tingling of both feet and lower legs. The feet felt cold and appeared pale. Pulsations could not be felt over the femoral, popliteal, posterior tibial, and dorsalis pedis arteries of both lower extremities. The condition of the legs and feet varied from time to time. Pulsations were present at times and absent at others. She

complained of intense pain most of the time. There was a slow improvement, but evidences of impairment of circulation of the extremities persisted. It was our impression that the disturbance consisted of arterial spasm secondary to thrombophlebitis. On several occasions there was a less evident abnormality of the circulation of the arms. In addition, there was what appeared to be a thrombosed vein at the umbilicus.

The quantities of chyle that were aspirated and reintroduced up to Feb. 15, the time at which the fat-free diet was terminated, have been enumerated. From Feb. 15 until her discharge from the hospital on June 15, a period of four months, 108,500 c.c. of chyle were removed from the abdominal cavity, 26,050 c.c. from the left pleural cavity, and of this latter amount, 11,100 c.c. were given intravenously. From March 10 to 17, heparin was administered intravenously by the continuous method, the clotting time being maintained at approximately twenty minutes. The clotting time on a previous examination was 3.5 minutes. The heparin was given with the hope that canalization of thrombosed veins would occur. No evidence of improvement resulted. No chyle was injected intravenously after April 13. Reasons for stopping the injection of chyle were that there was no apparent clinical improvement and that it became almost impossible to find a patent vein. Furthermore, the question arose as to whether or not the direct introduction of chyle into the blood stream might not be causing additional thrombosis.

As has been stated, the patient was discharged from the hospital on June 15, 1940. Her condition was less satisfactory than at the time of her admission more than six months previously. The extremities and face had become markedly emaciated. Chyle continued to accumulate, at least in the peritoneal cavity, as rapidly as at the onset. There was still evidence of disturbance of circulation of the legs and she frequently complained of pain.

It has now been almost a year since the patient returned to her home. Her condition has not changed markedly during this time. She is able to be up for short periods but tires very easily. Fluid has continued to accumulate in the peritoneal cavity from which it is removed once or twice weekly. The average quantity removed per day has been 1 liter. During the approximately eighteen months that the patient has been ill, more than 500 liters of chyle have been removed from the pleural and peritoneal cavities.

CHEMICAL STUDIES

In view of the probable disturbances in lipid metabolism and plasma protein concentrations entailed by the loss of chyle rich in lipid and containing a moderate quantity of protein, a rather extensive chemical investigation of the chyle and plasma was undertaken.

In obtaining the data reported here, all lipid determinations were made using the procedure of Kirk, Page and Van Slyke[4] with the following modifications: (a) extraction of lipids at room temperature as given by Boyd;[5] (b) substitution of 0.18 c.c. of saturated aqueous solution of sodium hydroxide plus 2 c.c. of ethyl alcohol for the procedure given by Kirk and co-workers for the saponification of total cholesterol; and (c) substitution of the procedure of Man[6] for the evaporation of the alcohol-ether extract prior to extraction with petroleum ether. The observed free cholesterol values are too high and may be corrected[7] by multiplying by 0.8. The total proteins and albumin were determined by a modification of Howe's method.[8] The determinations of colloidal osmotic pressure were made using the method of Wells.[9]

TABLE I

RECORD OF THORACENTESIS, PARACENTESIS, AND INTRAVENOUS CHYLE INJECTION

DATE	THORACENTESIS (C.C.)	PARACENTESIS (C.C.)	CHYLE TRANSFUSION	DATE	THORACENTESIS (C.C.)	PARACENTESIS (C.C.)	CHYLE TRANSFUSION
12/ 4/39	500			3/4	1,600	4,300	
12/ 5/39		80		3/5	2,700		
12/ 7/39	600		500	3/12	1,000		1,000
12/ 9/39	600		600	3/18	1,000		1,000
12/11/39	500		500	3/19		8,500	
12/14/39		1,800		3/20	1,000		1,000
12/19/39	1,000		1,000	3/25	1,000		1,000
12/21/39		3,200		3/28		8,100	
12/28/39	800		800	4/ 1	1,000		1,000
12/29/39		7,000		4/ 3	3,000		1,000
12/30/39	900		900	4/ 5	1,000		1,000
1/ 2/40	550		550	4/ 7		9,500	
1/ 4/40	800		525	4/ 9	100		100
1/ 9/40	950		950	4/12	1,000		1,000
1/10/40		3,500		4/13	1,000		1,000
1/12/40	500		500	4/14		7,000	
1/16/40	590		590	4/19		6,000	
1/19/40	700		700	4/26		6,700	
1/20/40		3,800		5/ 3	1,000		
1/21/40	330		330	5/ 6		6,000	
1/23/40	960		960	5/12		6,000	
1/24/40		3,350	550	5/16	1,250		
1/25/40	1,750			5/19		5,000	
1/30/40	430		430	5/24	2,100		
2/ 1/40	1,900	3,500		5/27		7,000	
2/ 6/40		3,500		6/ 2		6,000	
2/ 7/40	700			6/ 4	1,700		
2/15/40	1,000		1,000	6/ 7		8,000	
2/16/40		5,000		6/14		7,000	
2/19/40	1,000		1,000	6/15	2,100		
2/24/40	500						
2/25/40		8,400					
2/26/40	1,000		1,000		42,110	138,230	22,485

TABLE II

CONCENTRATION OF LIPIDS IN FLUID FROM THORAX (MG. %)

DATE	FREE CHOLESTEROL	ESTERIFIED CHOLESTEROL	RATIO OF ESTERIFIED TO FREE CHOLESTEROL	LIPID PHOSPHORUS	PHOSPHATIDE	TOTAL LIPID CARBON	NEUTRAL FAT	TOTAL LIPIDS
12/ 4/39	22	41	1.85	3.1	73	1,075	1,268	1,432
12/ 9/39	26	43	1.65	1.2	51	720	798	948
12/28/39	21	40	2.00	3.0	70	466	457	616
1/19/40	19	60	3.16	3.4	80	403	330	530
1/25/40	18	42	2.33	3.4	81	377	330	500
1/30/40	22	28	1.27	3.9	92	531	545	706
2/ 1/40	18	43	2.39	2.7	64	513	523	678
2/15/40*	18	29	1.61	3.9	92	842	958	1,117
2/26/40	27	35	1.30	8.0	189	1,980	2,353	2,628
3/ 5/40	23	39	1.70	5.4	128	1,579	1,876	2,093
3/12/40	28	46	1.64	13.2	310	3,177	3,810	4,226
3/18/40	36	41	1.14	13.0	306	3,108	3,721	4,132
4/ 1/40	16	51	3.19	9.8	231	2,572	2,768	3,101

*Drawn day after 500 c.c. of cream were given to patient.

From Table I it will be seen that over a period of approximately six months 180,300 c.c. of chylous fluid were removed from the thorax and peritoneum, while 22,500 c.c. were returned by intravenous injection. The lipid distribution in samples of these fluids drawn at various times is found in Tables II and III. As stated previously, from Dec. 3 until

TABLE III

CONCENTRATION OF LIPIDS IN FLUID FROM PERITONEUM (MG. %)

DATE	FREE CHOLESTEROL	ESTERIFIED CHOLESTEROL	RATIO OF ESTERIFIED TO FREE CHOLESTEROL	LIPID PHOSPHORUS	PHOSPHATIDE	TOTAL LIPID CARBON	NEUTRAL FAT	TOTAL LIPIDS
12/ 5/39	23	43	1.87	2.7	63	828	926	1,085
12/15/39	21	43	2.05	1.1	25	378	375	494
12/21/39	22	40	1.82	2.2	52	346	314	456
1/24/40	34	50	1.47	4.0	94	619	605	818
2/ 1/40	23	48	2.09	2.2	51	489	487	642
2/ 6/40	20	36	1.80	3.1	73	588	624	778
2/16/40*	27	47	1.74	5.2	122	1,116	1,250	1,478
5/ 6/40	20	49	2.45	6.5	153	2,310	2,803	3,059

*Drawn day after 500 c.c. of cream were given to patient.

Feb. 8, the patient was on a fat-free diet, which, by calculation, contained less than 5 Gm. of fat per day; and from Feb. 8 to 15 she was on a low-fat diet which contained approximately 40 Gm. of fat per day. After Feb. 15 the patient received the usual hospital diet calculated to yield 3,000 calories. While the patient was on a fat-free and low-fat diet there was a marked decrease in the total lipid concentration of the chylous fluids. This decrease was due largely to the neutral fat fraction, since there was no consistent decrease in the other lipid fractions. When the patient was removed from the low-fat diet there was a sharp and marked increase in the total lipid concentration of the chylous fluid, which is due not only to the neutral fat but also to the phosphatide fraction.

From the data given in Table IV it will be seen that the concentration of the various plasma lipid fractions remained remarkably constant throughout the period of observation. Whether this is due to a complete lack of effect of dietary regime, or whether it is due to the continual augmentation of plasma lipids by means of injections of chyle cannot be determined. It is of great interest that throughout the period of observation, the lipid concentrations are either only slightly below or within the normal range found by Page and his associates[10] for normal men. Another point of interest is the rapid removal of lipids from the blood after injection of chyle. Five and one-half hours after injection of chyle the concentration of the lipid fractions had returned to the preinjection level, with the exception of phosphatides which were still elevated.

TABLE IV

CONCENTRATION OF LIPIDS IN PLASMA (MG. %)

DATE	FREE CHOLESTEROL	ESTERIFIED CHOLESTEROL	RATIO OF ESTERIFIED TO FREE CHOLESTEROL	LIPID PHOSPHORUS	PHOSPHATIDE	TOTAL LIPID CARBON	NEUTRAL FAT	TOTAL LIPIDS
12/ 9/39	48	121	2.52	5.1	120	419	173	545
12/28/39	44	137	3.11	6.2	144	426	135	555
1/ 8/40	46	129	2.81	4.2	98	399	152	514
1/19/40	42	101	2.41	6.3	148	389	153	514
1/30/40	44	113	2.57	7.9	185	435	156	576
2/14/40	42	108	2.57	2.6	61	359	176	462
2/21/40	53	113	2.13	6.0	140	450	206	590
3/19/40	48	127	2.65	3.1	72	389	163	498
4/ 1/40*	54	169	3.13	3.3	77	470	181	598
4/ 1/40†	46	128	2.78	9.6	226	1,328	1,268	1,756
4/ 1/40‡	54	118	2.19	6.5	152	447	181	587

*Drawn just before injection of chyle.
†Drawn immediately after injection of 1,000 c.c. of chyle.
‡Drawn 5½ hours after injection of chyle.

The data obtained for total protein, albumin, and osmotic pressure will be found in Tables V, VI, and VII. There is no significant difference in the protein concentration of fluid from the thorax and that from the peritoneum. The average concentration in the former was 3.16 per cent and in the latter 3.08 per cent. The albumin-globulin ratios were quite variable, but with one exception they are always above 1.5. None of the variations in diet had an effect upon the concentration of protein in the fluids. The results obtained for serum proteins are of interest, in that in spite of a moderately high protein diet (75 to 80 Gm. per day) and continual injection of chyle the serum proteins and serum colloidal osmotic pressure progressively decreased. Both were certainly approaching a critical level. This decrease must be attributed to the enormous loss of protein in the chyle which was removed but not returned to the circulation.

TABLE V

PROTEIN DATA ON FLUID FROM THORAX

DATE	TOTAL PROTEIN %	ALBUMIN %	GLOBULIN %	A/G RATIO	OSMOTIC PRESSURE DETERMINED MM. H_2O
12/ 4/39	3.38	2.11	1.27	1.66	
12/ 9/39	3.48	2.08	1.40	1.49	
12/28/39	3.22	2.31	0.91	2.54	
1/19/40	3.11	1.90	1.21	1.57	
1/25/40	2.78	2.17	0.61	3.56	112
2/ 1/40	3.10	2.04	1.06	1.92	150
2/15/40	3.02	1.91	1.11	1.72	
2/26/40	2.72	1.86	0.86	2.16	
3/ 5/40	4.55	2.63	1.92	1.37	
3/23/40	3.40	1.55	1.85	0.84	
4/ 1/40	2.05	1.87	0.18	10.39	

It has been assumed, in some reports, that a limitation of the fluid intake and dietary fat would reduce the formation of chyle, but there has been no quantitative evidence to support this assumption. The patient reported here was maintained on a fat-free diet for sixty-five days during which time a total of 44,790 c.c. of fluid were withdrawn for an average of 689 c.c. per day. For a period of sixty-three days, when the patient received the regular hospital diet, a total of 75,700 c.c. of fluid were withdrawn for an average of 1,202 c.c. per day. This apparently supports the assumption, and there is no doubt but that the chyle formation is affected by a low-fat intake. However, in interpret-

TABLE VI

PROTEIN DATA ON FLUID FROM PERITONEUM

DATE	TOTAL PROTEIN %	ALBUMIN %	GLOBULIN %	A/G RATIO	OSMOTIC PRESSURE DETERMINED MM. H_2O
12/ 5/39	3.79	2.54	1.25	2.03	
12/21/39	3.53	2.98	0.55	5.42	
2/ 1/40	2.79	1.91	0.88	2.17	134
2/16/40	2.89	2.18	0.71	3.07	119
5/ 6/40	2.39	1.64	0.75	2.19	

TABLE VII

PROTEIN DATA ON SERUM

DATE	TOTAL PROTEIN %	ALBUMIN %	GLOBULIN %	A/G RATIO	OSMOTIC PRESSURE DETERMINED MM. H_2O
12/ 9/39	6.36	4.06	2.30	1.77	
12/28/39	6.65	4.05	2.60	1.56	
1/19/40	5.57	3.09	2.48	1.25	
1/30/40	6.10	---	---	---	278
2/ 1/40	5.04	2.98	2.06	1.45	268
2/14/40	5.90	3.79	2.11	1.80	230
2/16/40	5.03	3.11	1.92	1.62	220
3/18/40	4.51				218
3/19/40	4.05	---	---	---	228
4/ 1/40	4.70	3.93	0.77	5.10	220

ing these results another factor must be considered. During most of the time when the usual diet was being given the serum colloidal osmotic pressure was much lower than during the period of a fat-free diet. On three occasions the venous pressure was found to be 250, 262, and 230 mm. of water. Thus there was little margin between the venous pressure and colloidal osmotic pressure, so that the net filtration from the capillaries was probably greatly increased, thereby increasing the volume of lymph.

DISCUSSION

The interval between the injury to the patient and the evidence of the accumulation of chyle in the pleural and peritoneal cavities was five

weeks. In analyzing the histories of thirty-three patients with traumatic chylothorax, Shackelford and Fisher[11] found that this interval is most commonly four days but that it varied from two days to six weeks. The collection of chyle in both the pleural and peritoneal cavities is somewhat against trauma as the etiological agent. The absence of a penetrating wound does not exclude trauma as the cause. Most instances of traumatic chylothorax have followed crushing injuries, falls from a height, and blows on the chest.

The most common cause of nontraumatic chylothorax is malignancy. Despite a careful search, no evidence of malignancy was found in our patient. The fact that she is alive more than eighteen months following the onset of this disorder is evidence against a metastatic tumor as a cause of the blockage. Other causes of nontraumatic chylothorax include tuberculosis and venous thrombosis. Yater[1] has considered these and other etiological agents in detail. The findings at operation, i.e., thrombosis of the internal jugular vein, and the subsequent disturbances of the circulation of the extremities which were probably due to thrombophlebitis, lead us to believe that the most likely cause for the chylothorax and chyloperitoneum in our patient was multiple venous thrombosis. It is possible that the thrombosis of the internal jugular vein was secondary to traumatic rupture of the thoracic duct, but it appears more likely that the thrombosis was primary rather than secondary. This explanation is more compatible with the finding of evidence of thrombosis elsewhere in the body.

It is well known, furthermore, that the lymphatic system as well as the blood vascular system is abundantly supplied with collateral channels. The thoracic duct of man may be ligated and other lymph vessels will enlarge sufficiently to conduct the lymph to the venous system. It is usually impossible in dogs to cause total lymph blockage by the use of multiple stage operations in which many lymph vessels are ligated or destroyed. On the other hand, Blalock, Cunningham, and Robinson[12] found that chylothorax developed in approximately one-half of the dogs and cats in which the superior vena cava was occluded by a ligature. If the death of these animals was prevented by the aspiration of the chyle, usually other lymph vessels would enlarge with the passage of time and the chyle would be returned to the venous system.

It is possible that the lymph of this patient possessed some property which caused an injury to veins at the points of junction of the lymphatic and venous systems. Furthermore, it is quite possible that the reinjection of chyle resulted in a greater degree of venous thrombosis than would have occurred otherwise. Although the observation may not be pertinent to this discussion, Johnson and Freeman[13, 14] noted the existence in dogs of a hemolytic agent in lacteal lymph and to a lesser extent in thoracic duct lymph during the absorption of ingested fat. We found no evidence of hemolysis after the injection of chyle into the

vascular system of this patient. Since we had some doubts as to the advisability of injecting intravenously large quantities of chyle, Dr. Emmett Holt[15] was consulted, and it was his opinion that the introduction of the patient's own chyle would not be more dangerous than the use of emulsified fat provided the particle size was 1 micron or less with only an occasional particle as large as 3 microns.

One may find in the literature many analyses of chylous effusions in which methods with varying degrees of refinement were used. The reports of Harrel, Street, and Reiser[16] and Robinson and co-workers[17] are the most complete as far as lipid fractions are concerned. Harrel and his co-workers give a complete lipid analysis of fluids obtained from the right and left pleural cavities and peritoneal cavity. Robinson and co-workers determined the lipid fractions of fluids obtained from animals in which the superior vena cava had been ligated. Cookson and Slade[18] report very complete analytical data on a sample of chyle obtained from a patient.

We have found only one report in which the effect of treatment on the composition of a chylous effusion was studied. Schaefer[19] studied the effect of a fat-free diet in which the proportion of carbohydrate and protein was varied. The fat content of the chyle progressively decreased but variations of the dietary protein or carbohydrate produced no consistent effects.

In no previous instances have the effects of treatment (low-fat diet and injection of chyle) upon the chyle and serum proteins and upon the plasma lipids been determined. The plasma lipids were maintained at a normal or slightly less than normal level. We were unsuccessful, however, in preventing a rather critical decrease in the serum protein concentration and serum colloidal osmotic pressure by the treatment that was used. Over a period of six months there was a net loss of chyle of 158,000 c.c. with an average protein content of 3 per cent, or a net loss of 4,740 Gm. of protein, which is approximately 25 Gm. per day. A large percentage of this was albumin. Madden and Whipple[20] have recently reviewed the source, production, and utilization of plasma proteins. They state that normal dogs have sufficient protein reserves to form a quantity of plasma protein one to two times the amount normally present in the circulation. Once this reserve is depleted the subsequent formation of plasma proteins is almost entirely dependent upon the quantity and quality of the dietary protein. Unfortunately records of food consumption were not kept in the case reported here, but it is very probable that the protein consumption was less than 80 Gm. daily. The declining serum protein concentration indicates that the protein consumption was insufficient to maintain the plasma protein level by regeneration. It would have been interesting to try the effect on regeneration of a diet containing gelatin, cystine, and tyrosine, which was found by Whipple and his co-workers to be very efficient in

animal experiments. The protein loss is very significant from the nutritional viewpoint and also in consideration of lymph production and it is our belief that it is more important in the bodily economy of the patient than the lipid loss. When it is realized that during her nineteen months of illness approximately 550 liters of chyle have been removed from the patient, representing a loss of approximately 16,000 Gm. of protein, it is surprising that her downhill course has not been even more rapid.

In reviewing our experience with this patient, it is evident that at least the following factors are in need of further study: (a) the effect of the dietary protein upon the regeneration of plasma proteins in patients subjected to a continuous loss of protein, as in the case here reported; (b) the possible efficacy of frequent plasma transfusions as a means of treatment; and (c) the effect of repeated injections of chyle upon the clotting time of the blood and upon the endothelium of the vascular system.

In summary, the clinical course of a patient with chylothorax and chyloperitoneum has been described. The effects of a fat-free diet and of reinjection of the aspirated chyle have been noted and the significance of the alterations has been discussed.

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THE SURGICAL MANAGEMENT OF VARICOSE VEINS: IMPORTANCE OF INDIVIDUALIZATION IN THE CHOICE OF PROCEDURE*

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VARICOSE veins have long been classified as a so-called minor surgical condition and in consequence their care in many cases has been relegated to residents and other younger surgeons. In only rare instances has a more experienced surgeon devoted enough time to the study of this subject to become well acquainted with the variations these cases may present. As a result, either a stereotyped operation is performed or the patient is treated by a physician who, not being a surgeon, has no choice but to use some medical treatment such as the injection of sclerosing solutions. While these latter treatments may have their place, only too often when a doctor has only one means of treatment at his disposal, he will use only that method.

The interest of one of us (H. N. H.) was aroused in this subject from being personally afflicted with the condition and from having had personal experience with sodium morrhuate injections, and later, more successfully, with surgical operative treatment. The present series represents the operations performed by the senior author (H. N. H.) during the year 1940 (Jan. 13, 1940, to Jan. 12, 1941). Operations on three of the sixty-three patients were done by two of the senior author's assistants under his direct supervision and using his methods. During this period a substantial number of other operations performed by other surgeons in the Henry Ford Hospital is not included in this series. The cases have not been followed long enough to observe the ultimate results. The present series does not, therefore, at all pretend to be a follow-up report, but merely is a presentation of the methods used by one of us over a one-year period.

DIAGNOSTIC MEASURES

The following tests were used in diagnosis and determination of the type of therapy to be used:

1. *Inspection and Palpation.*—In general, cases with visible or palpable veins above the knee were considered as unsuitable for injection alone. The presence of edema was considered a contraindication to all modes of therapy (injection or ligation) until the edema was controlled.

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Very superficial veins are stripped with difficulty as they are friable and attached to the dermis so that if they are to be removed, excision is preferable to stripping.

2. *Schwartz Test.*—Percussion with palpation of the impulse down the vein is often considered to be a sign of incompetent valves, but may occur in normal veins. This method, however, helps in tracing the course of veins, especially in obese patients.

3. *Perthes Test.*—

a. With Tourniquet.—With a high tourniquet, if the veins become more prominent on walking, a deep thrombosis is suspected. However, if there is a localized thrombosis below the tourniquet, the test would not necessarily rule it out. Similarly, however, if the test is normal, even if there is a localized deep thrombosis, unless by chance the detouring superficial veins just adjacent to it are operated upon, no harm will probably result. As a diagnosis before injection therapy, the theoretical objection is more valid.

b. With Tight Rubber Bandage From Ankle to Thigh.—This will detect even a localized deep obstruction (tight bandage test of McCallig and Heyerdale, 1940).

4. *Trendelenburg Test.*—To avoid confusion as to "positive" and "negative" we use the terms normal, abnormal, and doubly abnormal. Normal means no filling from above after tourniquet release, abnormal means filling only from above indicating fossa ovalis leakage, while doubly abnormal means filling from both above and below indicating fossa ovalis leakage plus lower incompetent perforators.

5. *Mahorner-Ochsner Test (1938).*—With a tourniquet high in the thigh complete emptying of the varicose veins on walking indicates incompetency only at the fossa ovalis. A control should always be done with the patient walking without a tourniquet as we have seen at least three patients where if this had not been done, the results would have been misleading. If the high tourniquet does not produce complete "walking-emptying," it is placed progressively lower until such an effect is obtained. This marks the site of the lowest incompetent perforator. The two-tourniquet test of Pratt (1939) appears to be of value, but we did not use it in the present series of cases.

6. *Harkins Test.*—This test, which we have also called the local Mahorner-Ochsner test, gives a horizontal as well as a vertical localization. For example, in a case where the Mahorner-Ochsner test shows the lowest perforator to be just above the knee, but yet the exact place on the circumference of the leg where this perforator is to be found is unknown, the following test is performed. The examiner sits on a very low stool at the side of the patient and places the middle finger of both hands on the most suspicious vein at this level. This is usually away from him over the medial condyle. His hands loosely surround the leg and the two thumbs are then placed for counter pressure on a relatively

vein-free area over the lateral condyle of the femur. The patient is instructed to keep the opposite foot motionless but to step alternately forward and backward five times with the other foot, the leg of which is being held all the time. An observation is then made, and in cases where the vein pressed upon is the chief culprit, as good emptying of the varices below will be obtained as with the tourniquet at this level. In nine patients five good positive tests have been obtained and in two, pressure with one finger combined with "weight-bearing leg swinging" caused complete emptying below the compressed vein. Subsequent operation revealed an incompetent perforator at this point.

7. *Coughing Impulse Test.*—Adams (1939) pointed out the importance of straining pressures in varicose veins stating: "We have felt that the Trendelenburg test, as usually performed is not a satisfactory test of valvular competence, inasmuch as it considers standing pressures only." He observed patients whose valves were competent to standing pressures and so exhibited a normal Trendelenburg, yet whose valves were incompetent to the added pressure of straining and promptly exhibited an abnormal Trendelenburg when this factor was introduced. Consequently Adams speaks of a valve being relatively competent when it stands the ordinary pressures of erect posture but permits reverse flow under the added effect of strain. If the fingers of the palpating hand of the examiner be placed over the saphenous opening of the patient in the standing position, back flow in the incompetent cases is readily detected as a palpable venous thrill when the patient coughs or strains. Adams finally concludes that "pressure and not the reversal of flow is the dilating factor."

Reviews of the pathology of varicose veins and of the physiologic basis of the various tests have been given by Freeman (1939), Oehsner and Mahorner (1939) and Heller (1940).

INJECTION TREATMENT

In our series of about 80 patients with varicose veins seen in 1940, only about 5 were advised to have injection alone. About 10 were advised to have ligation, but did not accept operation and the remaining 63 form the basis of this report. Two or three patients with active phlebitis were given palliative treatment.

The injection method was especially popular in the decade 1920 to 1930 when a reaction against the operative treatment occurred. The two chief objections to the injection treatment are the occurrence of reactions and lack of permanency of the method. Reactions have been reported by Kettel (1931), Ritchie (1933), Zimmerman (1934), Praver and Becker (1935), Lewis (1936), Dale (1937), McCastor and McCastor (1937), Shelley (1939), Holland (1939), Kadin (1940), and others. The use of injections is especially supported at the present time by the dermatologists, such as Isaak (1939, 1940). Writing in the former

year, this author stated "today it cannot be denied that the treatment of varicose veins by injections has almost replaced surgical methods." A view in opposition to this was taken by Dean and Dulin (1940) and one of us (H. N. H., 1940).

The old thrombogenic type of injections has been largely replaced by the sclerogenic type. Sodium morrhuate has been used exclusively in our series with no reactions. We have since had one transient reaction in a case not included in this series.

Sodium morrhuate was first used as an injection treatment for varicose veins by Higgins and Kittel (1930), who reported favorably on its use in 187 patients treated at the Royal Northern Hospital, London. Barber (1930) used this method shortly afterward. Ritchie (1933), of Edinburgh, used this method in a large series of cases of pregnancy and about this time sodium morrhuate became popular in the United States.

We have always tried to allow no more than seven days to elapse between large injections. If the patient stays away longer than seven days, the series is begun over again with an initial small (1 c.c. or less) desensitizing dose. This practice was based on the principle that anaphylactic sensitivity usually takes longer than seven to ten days to develop. Holland's (1939) 3 cases of reaction to sodium morrhuate all occurred in patients who had had previous injections of the substance, but in whom an interval of four weeks or more was allowed to elapse before giving a 2 c.c. dose. Ritchie's (1933) case with reaction followed an injection of 2 c.c. given ten days after a first injection.

Only 1 case was treated by the method of segmental sclerosis (injection of sodium morrhuate into the distal cut end of the saphenous vein through a long ureteral catheter) as advised by Pratt (1939). The results in this 1 case were good. We have had no experience with the twin injection technique of Maingot for vein injection as described by Scott (1930) and Fowlie (1940).

Because of failures with injection alone in previous cases, we have used operative methods in most of our cases seen in 1940. In general, injection alone was reserved for cases with (1) no palpable superficial veins above the knee and (2) a normal Trendelenburg reaction. With regard to the first criterion it is of interest that Mårtensson (1938) found that relapses developed in all his cases (55 in all) in which the insufficiencies of the veins extended above the lower third of the thigh. Ochsner and Mahorner (1937) reported a 57 per cent recurrence rate following injection alone while other writers reported rates all the way from 0 to 98 per cent.

Much of the benefits of injection so far as a low mortality from embolism are concerned may be attributed to the fact that injections are given to ambulatory patients while operations, at least before 1930, were done on bed patients. Westerborn (1936-37) reported the inci-

dence of fatal pulmonary embolism following different methods of vein treatment in Sweden as follows:

1. *Operation,* 0.26 per cent (6,994 cases operated upon from 1921 to 1925 with 18 deaths from embolism).

2. *Injection plus operation,* 0.33 per cent (1,200 cases treated with 4 deaths from 1928 to 1934).

3. *Injection,* 0.036 per cent (30,000 treated cases with 11 deaths from 1927 to 1934).

It is to be noted that the operation series was all done before 1925, and hence when bed rest for several days afterward was the rule.

Postoperative Injections.—In our series of 63 patients, 28 received postoperative injections and the average number of injections per case was 4.7. Slevin (1940) reported that in his series of 73 patients injected after vein ligation, 494 injections were given, an average of 6.76 per patient. Dean and Dulin (1940) opposed injection therapy without preliminary high ligation. In 600 cases treated at the University of Iowa by injection alone, there were 2 deaths from pulmonary embolism. These authors adopted the method of using injections only after high ligation. Taylor (1940) also advised injection only after preliminary ligation.

Our technique of injection postoperatively is to wait about ten days before giving an initial desensitizing dose of 0.5 to 1.0 c.c. of 5 per cent sodium morrhuate. An interval of no longer than a week is then allowed, otherwise the series is begun over with a new desensitizing dose. The dosage is worked up to, but never exceeds 5 c.c. In large veins, we use what we call the "elastoplast technique" of injection. A piece of elastoplast four inches by six inches is slit vertically for 2 cm. in its center. It is then spread tight over the site of injection, the slit now forming an oval opening through which the injection can be given. All patients rest horizontally for twenty minutes after injection and then walk away from the clinic.

Injection at Time of Operation.—Only 3 patients in our series received injections into the distal end of a cut vein at the time of operation. Two of these were done by the usual syringe and needle method, while the other was treated with the ureteral catheter technique of Pratt (1939). The results in this latter case were good. These 3 cases were early in the series and since then this method has been abandoned for four reasons:

1. The pain of the injection is far worse than that of the operation and is apt to cause the patients to go to bed with consequent danger of embolism.

2. Injection into a distal segment is not effective unless large amounts of sodium morrhuate are used (e.g., 5 c.c.). If these are used as an initial dose, a reaction may occur. If the patient is desensitized previous to operation, inflammation of the vein may make the operation difficult.

3. Secondary incisions low down on the thigh and on the leg cannot be made after distal injections, as otherwise the injected fluid will leak into these lower wounds.

4. If time is allowed to elapse for the veins to collapse, less fluid need be injected later.

Hawkes and Hewson (1940) also do not inject at the same time as they ligate. They stated that following ligation the veins usually collapse, so that by waiting two weeks they are dealing with a smaller vein and a smaller thrombus will be formed. In patients with bilateral veins, they injected one at the time of operation and allowed a wait of two weeks before injection with the other. The ultimate cosmetic result averaged better where the injection followed a period of waiting. These authors also point out the second objection to injecting at the time of operation; namely, that it may cause so much pain as to necessitate bed rest.

OPERATIVE TREATMENT

Operative procedures on varicose veins may be listed in outline form as follows (complete references in Ochsner and Mahorner):

A. *Before Modern Injection Period.*

1. Puncture (Hippocrates, 500 B.C.).
2. Tearing with hook (Galen, 201).
3. Double ligation and section in thigh (Paulus Aegineta, 690), (Paré, 1590), (Trendelenburg, 1890).
4. Removal by dissection (Albucasis, 1106), (Madelung, 1884).
5. Percutaneous ligation (Davat, 1937).
6. Multiple ligations and sections (Schede, 1877).
7. Circular incision.
   a. Single (Peterson, 1893).
   b. Multiple (Rindfleisch-Friedel, 1908).*
8. Stripping.
   a. Internal wire (Keller, 1905).
   b. External stripper (C. H. Mayo, 1906).
   c. Internal stripper (Babcock, 1907).

B. *After Modern Injection Period.*

1. High ligation at fossa ovalis (Homans, 1916).
2. Similar high ligation as ambulatory procedure (de Takats, 1930).
3. High ligation plus retrograde injection.
4. High ligation plus conservative excision at site of incompetent perforators (Homans, 1916).
5. High ligation plus conservative excision or stripping at site of incompetent perforators (Harkins and Schug, 1941).

*This method is, according to Ochsner and Mahorner (1939), "one of the most atrocious crimes a heavy-handed surgeon ever inflicted on his patients." After excision in the thigh, a circular incision, beginning at the knee and ending at the ankle is passed around the calf four to seven times. The ultimate result looks like a cut rubber tree trunk.

Importance of Ambulatory Treatment.—The two periods listed separately above might also be termed the "postoperative bed rest" period and the "ambulatory" period. High mortality from embolism caused the early operative methods to be discredited. Berntsen (1927), in discussing the results of extirpation of varices in 376 patients, reported embolism in 7.2 per cent and a mortality rate of 0.7 per cent. All of these patients were operated upon before de Takats (1930) introduced operation as an ambulatory procedure. Dean and Dulin (1940) and others stress the importance of ambulatory treatment in these cases.

The operation of high ligation of the saphenous vein as an ambulatory procedure was described by de Takats (1930), who reported 50 such operations. In 1933, de Takats and Quillin reported 150 additional cases, making a total of 200 with 1 death from sepsis. No case of embolism occurred and de Takats and Quillin concluded that "two factors, namely, the ambulatory management and the shortness of the proximal stump, are important in the prevention of embolism." The additional technical point of ambulatory treatment, we believe, has altered the entire results of operative management of varicose veins. The results as far as embolism is concerned have been so good that nine years after de Takats' original paper on the subject, Ochsner and Mahorner (1939) stated that no deaths from this cause following operation "have been reported when ambulatory regimen has been used."

Multiple Supplementary Ligations.—It was soon found that multiple ligations were not effective unless a high ligation was performed at the fossa ovalis with division of all the branches of the saphenous vein at this point. Similarly, more recent authors have found that in cases with additional leaks below the fossa ovalis, additional incisions must be made. It is our policy always to ligate at the fossa ovalis, and often to supplement this procedure with additional ligations below. Thus, these multiple ligations below are always supplementary to the fossa ovalis ligation. Essentially this procedure has been advised by Homans (1916), Ochsner and Mahorner (1939), Wright (1940), Rees (1940), and many others. Hawkes and Hewson (1940) do a "two-point" ligation, high and at the site of the lowest perforator. It seems to us that this may not be adequate and that an excision of the vein to eliminate some of the perforators between may be advisable. Slevin (1940) reported that following high ligation alone, he had a recurrence rate of 17 per cent, while with multiple ligations it was only 4 per cent. He mentions, however, that in some of the earlier cases of high ligation, all of the branches of the saphenous vein at the fossa ovalis were not ligated.

Vaughn (1940) stated that he had never done a bilateral ligation as one operative procedure. In our series, 35 of 63 patients (56 per cent) had bilateral ligations performed at one sitting and nothing that occurred in this experience would cause us to abandon treatment of both legs simultaneously.

The Lesser Saphenous Vein.—Many authors such as Wright (1940) have written vaguely about the importance of the lesser saphenous vein in causing varicose veins. Few statistics on this subject are available. Slevin (1940) reported that of 100 extremities ligated, in 5 instances (5 per cent) the lesser saphenous was ligated. Slevin also mentions that the lesser and greater saphenous often communicate. In our series of 98 legs, only three definitely enlarged lesser saphenous veins were operated upon (an incidence of 3 per cent). In all other cases it was searched for in the popliteal fossa by inspection and palpation and in seven instances the popliteal fossa appeared so suspicious that an incision was made which revealed no enlarged vein. In the cases where a definite vein was found, however, it was quite large (8 mm. or more) in diameter, but smaller than the vein shown in Fig. 5 of Adams' article (1940), and definitely perforated the deep fascia. Furthermore, intentional release of a clamp on the central end revealed marked bleeding.

Adams (1940) stated that with one exception, he had "not observed any cases of varicosities involving the short saphenous veins in which a definite communication with the long saphenous was not present and we are of the opinion that this rather than the deep femoral vein is the usual mode of transmission of pressure to the short saphenous system." We can agree with Adams in his anatomic observation, but not in his physiologic conclusion. In most cases the lesser saphenous forms the lateral branch of a *Y*, the medial branch arching from above and anteriorly over the medial condyle of the femur from the greater saphenous. The two unite and go down the back of the calf, the united vein soon branching itself. However, as stated above, in cases of enlarged lesser saphenous veins, we have found a marked flow of blood to come from the central end and in no case have we found valves closer than 3 cm. from the perforation through the fascia.

OPERATIVE TECHNIQUE

1. *Hospitalization.*—Of the 63 patients, operation was performed on 62 in the operating room and on 1 in the outpatient clinic. This latter patient developed a hematoma at the fossa ovalis incision. While we believe this operation can be done in an outpatient clinic, we advise that it be done in an operating room. On the other hand, of the 63 patients, 51 were operated upon as outpatients. Of the 12 remaining, 2 were already in the hospital, 1 entered voluntarily before operation, and 5 entered after operation because of their condition (bleeding, prolonged operation, faintness, general anesthesia, etc.). The other 4 patients that entered the hospital did so for economic reasons to obtain hospital and medical insurance to which an outpatient visit would not have entitled them.

2. *Anesthesia.*—All but 1 patient was operated upon under local anesthesia. This 1 patient was an extremely excitable woman of whom

an exception had to be made. Within a few hours after operation, however, she was forced to walk just as though she had been operated upon under local anesthesia. One-half per cent novocain without adrenalin was used in practically all the local cases. No preoperative sedation was used in most of them as it was noted that after using opiates, the patients were apt to faint on adopting the ambulatory regimen. Furthermore, because of traffic dangers, the use of opiates was contraindicated in the outpatients.

3. *Draping and Skin Preparation.*—If only fossa ovalis incisions were to be made, these could be done on both sides at one draping. Otherwise one leg at a time was draped and completed. Iodine was used as it did not wash off the gentian violet markings on the legs that were placed to indicate the site of incisions. An aqueous antiseptic (hexylchloro-M-cresol) was applied in the region of the genitals to avoid burning.

4. *Silk.*—Fine black silk was used in all cases for sutures and ligatures except of the central stump of the saphenous vein where a heavy ligature was used.

5. *Fossa Ovalis Incision.*—We tried the longitudinal incision advised by Ochsner and Mahorner (1939) but have come back again to the oblique incision. The longitudinal incision does not follow the lines of force; it bleeds more easily and is more apt to give rise to a subsequent hematoma; the medial flap tends to pull upward in the middle and the resultant scar is more marked even when approximation is guided by preoperative skin scratches. At the fossa ovalis we now use an obliquely transverse incision a fingerbreadth below and parallel to the femoral crease. Use of the palpated femoral pulse as the lateral end of the incision seems to be a better guide than marking the varix, which often is not visible, in the erect position. Especially in obese patients, as soon as they lie down, the relation of skin to deep tissues becomes distorted and the marks are apt to be misleading. As any medical student knows, however, the femoral artery lies just lateral to the vein and therefore to the fossa ovalis. The vein is found and identified. We have several guides to the vein other than experience. It is usually marked by the typical branches and it lies in the superficial fatty tissues while the femoral vein is at the same depth as the artery which can be palpated. In cases of doubt we lightly pinch the vein to note if the distal segment swells as it would if it were the femoral. Finally, except in cases of visible varices which are superficial, the vein is often much thicker walled than the femoral. At the most accessible point the vein is divided between clamps; the assistant then retracts only the lower margin of the wound, a little novocain is placed along each side of the vein and with a Mayo vein clamp the lower segment is followed down for about two inches in hopes of finding the descending femoral branch. If this is found, it and the vein are separately transfixed and the two-inch segment removed. Otherwise the

saphenous alone is so treated. The assistant then retracts only the upper margin of the wound and the lower stump is forgotten. The upper stump of the vein is followed up to where it enters the fossa ovalis, the lower border of which is marked in about 90 per cent of the cases by the visibly pulsating archlike superficial external pudendal artery. We have found that this technique of dividing the vein at the start of the operation renders exposure of the fossa ovalis much easier than the method of not cutting the vein until the end of the procedure. All branches are doubly clamped and ligated, attempting in all cases to get the three main ones (external pudendal, inferior epigastric, and circumflex iliac). In women the external pudendal often assumes great proportions and should be followed medially until it branches, ligating the two branches separately. The various anomalies at the region of the fossa ovalis which should be searched for and ligated have been pointed out by Stalker and Heyerdale (1940). The saphenous itself is then held up under only moderate tension and ligated even with the edges of the fossa with heavy silk. A fine silk transfixion suture is then placed just distal to the ligature so that no silk crosses the lumen of the proximal portion of the vein. The free portion of the proximal stump is then cut off distal to the transfixion suture. Fine silk is used for all ligatures and sutures except the one most proximal on the stump of the saphenous. In tying it, if too much pull is exerted on the vessel, the same error may be made as occurs in tying off a cystic duct under too much tension; i.e., looping up the femoral vein itself into the ligature as may be done with the common duct. The advisability of leaving a short stump is at once apparent. Kilbourne (1934) stated that high ligation "may cause a funnel-shaped blind pocket in the vein proximal to the ligature in which the blood stagnates allowing a thrombus to form." He stated that ligature has a mortality of 0.5 per cent but cited Schiassi who claimed 2,500 ligations without embolism.

A single silk suture is placed at the midpoint of the deep layer of the superficial fascia and the skin closed with interrupted silk. In these ambulatory patients we have found that end-on mattress sutures are the only ones that will hold the skin edges in approximation at all satisfactorily.

6. *Lower Incisions.*—These are made longitudinally except where they are to allow exit for the end of the stripper, in which case they are horizontal and only 1 cm. long. These incisions are made on the lines previously marked by gentian violet where incompetent perforators are suspected. The most usual site is over the adductor tubercle of the femur. It may be because the femoral vein has at this point just escaped from Hunter's canal that it so often gives a large perforating branch in this region. All branches are ligated and the main saphenous vein as high as possible at the upper end of the incision and as low as possible at the lower end is transfixed. A suture is inserted subcutaneously every 2 cm. to approximate the fascia and the wound closed with skin silk.

In our series, 217 incisions were made on 98 legs. On all but 1 leg, a fossa ovalis incision was made, so this made 120 incisions below the groin, an average of 1.3 per leg. We believe that a fossa ovalis incision and accompanying ligation should be done on every case where any operation is performed. We did not do it on this 1 leg (the second leg of a bilateral operation) because of the length of the operation. Only 28 patients had only fossa ovalis incisions and it is of interest to note that these all were during the first half of the period covered by this report. Thirty-one incisions were made below the knee (13 per cent of the total) and of these 29 were done during the second half of the series. It is thus seen that so far as operating below the groin and below the knee is concerned, we became much more radical as time went on.

7. *Stripping.*—When we began stripping as an ambulatory procedure, we were told that it was not feasible because of pain and hemorrhage. Neither of these fears was justified. Simple novocainization just under the skin is adequate for a practically painless stripping if the course of the vein has been accurately marked ahead of time. Furthermore, with elastoplast, no case of hemorrhage or hematoma occurred. We have, however, abandoned stripping the proximal six inches of the saphenous vein because the elastoplast cannot exert pressure at this level and one hemorrhage occurred above the compression. A Mayo vein stripper is used in all cases and with practice when a branch is reached it is identified, the stripper cut down upon, the branch doubly ligated and the stripping proceeded with. Even when a branch is torn, however, no hematoma has resulted with elastoplast. Visible veins are usually friable or attached firmly to the dermis and unsuitable for stripping. Finally, recent previous injections may cause stripping to be difficult. Otherwise, we substitute stripping for excision as much as possible as the cosmetic result is better. We have repeatedly noted that if a segment of vein is left behind between ligations, it becomes much more painful than the channel left by stripping such a vein. Nineteen patients had stripping, 15 of them during the second half of the series. Most stripping was done in the lower thigh and seldom below the upper fourth of the leg.

8. *Dressings.*—We have found that an extremely small piece of gauze, 1 by 3 inches, covered by a 2 by 6 inch piece of adhesive tape is much less apt to lead to infection of the fossa ovalis incision than bulkier dressings. The skin is always rubbed beforehand with ether to cause the adhesive to stick well. The lower incisions are dressed with small pieces of gauze and a roll of elastoplast from two inches below the lowest incision to two inches above the uppermost one.

9. *Postoperative Orders.*—Prime emphasis is placed on frequent walking and nothing is done to interfere with this. Consequently only aspirin is given as an analgesic. In fact, now that we do not use

injections at the time of operation, pain is not an important factor. All patients who had had injections sometime before operation stated that the operation hurt far less than an effective injection. The patients are informed of the "seven-hour rule": that they must not stay in bed longer than seven hours at one time for several weeks. If they wish to go to bed early and get up late, they must get up once in the middle of the night. They are not cautioned against standing, for fear that this will cause them to rest and also in the sincere belief that if they have been improved by the operation, that improvement begins at the time of operation and reversed blood flow on standing will no longer be a factor. The dressing is usually changed on the sixth day, and at that time one-third of the stitches are removed, the remaining coming out on the eleventh day, at which time postoperative injections may be begun if necessary.

ANALYSIS OF MATERIAL

This study consists of an analysis of operations of 98 separate lower extremities done on 63 individuals during a one-year period between Jan. 13, 1940, and Jan. 12, 1941. All procedures and operations were done by the senior author (H. N. H.) except 3, which were under his direct supervision. Forty-two of these patients have been rechecked in the past six weeks (Jan. 1, 1941, to Feb. 15, 1941) to determine the present condition of their veins and the status of their legs, as well as to obtain their own estimation of improvement or other alteration of their condition. Twenty-one patients were not contacted. This was probably due to the fact that some of the patients only lived or worked in Detroit for a short time and also to the fact that many of our patients came from some distance outside of the city. In the latter group we were able to get an approximate appraisal of results through correspondence.

The longest we have been able to follow any of these cases is 13½ months. Because of this a final conclusion cannot be drawn; however, we believe that the results obtained by our treatment merit presentation at this time.

TABLE I

VARICOSE VEIN SURVEY

(TOTAL NO. CASES, 63; NO. LOWER EXTREMITIES OPERATED UPON, 42)

SEX INCIDENCE		SIDE INCIDENCE	
Males	28	Left leg	56
Females	35	Right leg	42

Sex.—The group included 35 women and 28 men. Ochsner and Mahorner (1937) observed 247 women and 38 men, and Hawkes and Hewson (1940), 441 women and 159 men, so a preponderance of females seems to be the rule. The excess was less in our series in all probability because of the industrial nature of our clientele.

Age.—By far the largest proportion (63 per cent) of the patients was between the ages of 40 to 54 years, thus possibly lending support to Sicard's (1929) hormonal theory. It is more probable, however, that employment, economic factors, and progression of the disease played a role in causing persons of this age to seek attention. Hawkes and Hewson (1940) found a slightly smaller number to fall in this age group, 45 per cent of their patients being within the age group of 40 to 59 years.

Side.—The left leg was involved in 56 instances and the right in 42. On the right leg 125 incisions were made and on the left 92. Ochsner and Mahorner (1939) stated that neither side was involved more, while Steubner (1930), cited by Ochsner and Mahorner, found the right leg to be involved slightly more often, the opposite to our series. We operated upon 38 of 63 patients (60 per cent) bilaterally while Hawkes and Hewson (1940) operated upon 440 of 600 patients (76 per cent) bilaterally. An economic factor may have caused our percentage to be low.

TABLE II

VARICOSE VEIN SURVEY

AGE INCIDENCE (62 CASES)			DURATION OF SYMPTOMS (46 CASES)	
20-24 yr.	2		0- 4 yr.	2
25-29 yr.	2		5- 8 yr.	11
30-34 yr.	5		9-12 yr.	3
35-39 yr.	1		13-18 yr.	8
40-44 yr.	14		19-24 yr.	8
45-49 yr.	15	63%	25-35 yr.	10
50-54 yr.	11		36-45 yr.	3
55-59 yr.	5		46-55 yr.	1
60-64 yr.	3		Average	16.3 yr.
65-70 yr.	4			

TABLE III

VARICOSE VEIN SURVEY

	0	±	+	++	+++	++++*
Severity of presenting symptoms (42 cases):						
Pain	8	2	11	6	8	6
Swelling	5	0	8	14	8	6
Appearance	18	1	9	7	6	0
No. of cases of ulcer 22						
Postoperative severity of symptoms (42 cases):						
Pain	30	7	2	3	0	0
Swelling	26	10	6	0	2	0
Appearance	36	2	2	2	0	0
No. of ulcers present Feb. 21, 1941 2						

*These notations refer to the intensity of the symptoms: 0, absent; ±, trace; +, mild; ++, moderate; +++, marked; and ++++, severe.

Mode of Onset.—The onset was gradual in 30 cases, gradual with pregnancy in 3 more cases, and acute in 10 cases (2 of these cases occurred with milk-leg at pregnancy, 2 without milk-leg at pregnancy, 2 with thrombophlebitis following abdominal operation, and 3 were acute with ulcer, pain, or swelling).

Duration of Symptoms.—In 46 cases analyzed, the average duration of symptoms was 16.3 years.

Symptoms.—The three main symptoms were pain, swelling, and disfigurement as shown in Table III. The number of patients who had no other complaint than the appearance of the veins is surprising. Other symptoms did not always seem to be proportionate to the size of the veins.

Previous Injections.—Twenty-one patients had had previous injections, the average being 13.7 per patient.

TABLE IV

VARICOSE VEIN SURVEY

MODE OF ONSET OF SYMPTOMS (43 CASES)

Gradual		30
Gradual with pregnancy		3
Acute		10
With milk leg at pregnancy	2	
With pregnancy alone	3	
With thrombophlebitis after surgery	2	
With ulcer, pain, or swelling	3	

TABLE V

VARICOSE VEIN SURVEY

PREVIOUS TREATMENT (63 CASES)

SURGERY			INJECTIONS	
NO.	PLACE	DATE	No. of patients injected	21
1	H. F. H.*	1935	Average no. injections per patient	13.8
2	H. F. H.	1939	*Other methods of treatment:*	
2	Outside	1938	1. Elastic stockings	
1	Outside	1930	2. Ace bandages	
1	Outside	Unknown	3. Sooey and Unna paste boots	
Total	7 cases		4. Salves, ointments, pastes	

*Henry Ford Hospital.

Previous Operations.—Seven patients had had previous unsuccessful vein operations. Three of these were done in our own hospital and 4 elsewhere. In some instances it was difficult to tell what had been done previously, while in others the findings were extremely interesting. In 1 case one limb of a bifid saphenous had been ligated below the fossa ovalis. In another, the vein had recanalized after ligation. In another, a lesser saphenous had been overlooked. The most interesting case, however, and most recently operated upon was that done by an assistant resident in 1939. Dissection revealed that he had ligated the external pudendal where it entered the saphenous, evidently mistaking this point for the saphenofemoral junction. The ligature was still in place!

In our own series 1 reoperation was done (a lesser saphenous overlooked previously in one of our early cases), and 1 other was advised (an evident perforator near the adductor tubercle in one of our early cases).

TABLE VI

VARICOSE VEIN SURVEY

NO. OF INCISIONS MADE

Left leg	125	Incisions below knee (31% of total)	31
Right leg	92		
Total	217	Incisions below knee made prior to July 13, 1940	2

Stripping done in 19 cases
Prior to July 13, 1940, stripping in 4 cases

No. of postoperative injections:

No. of cases	27
Average no. injections per case	4.7

TABLE VII

VARICOSE VEIN SURVEY

POSTOPERATIVE COMPLICATIONS (63 CASES)

Stitch infections		8
Infected wounds		2
Seromas		2
Keloid formation		1
Postoperative bleeding		6
Severe, requiring reopening	3	
Hematomas	3	

POSTOPERATIVE COMPLICATIONS

Stitch Infections.—These occurred in 9 cases but were healed in all cases within seven days or less, except in 1 and that was healed within three weeks. In labeling these cases as infections, we used the strictest possible interpretation of the word and included all instances that did not heal 100 per cent primarily. Even if the wound edges healed primarily but yet the stitch holes exuded a drop of pus or fluid, the case was called an infection.

Infected Wounds.—Only two deep infections occurred and both of these followed hematomas and were well localized. Both of these occurred during the first half of the series and since during the second half we adopted better measures to prevent hematomas, we believe that infection is no longer an important factor. Both infected wounds healed without extruding the silk ligatures.

Seroma.—Only two wounds developed a seroma and both of these healed promptly after evacuation.

Silkosis.—*Only 3 wounds developed silkosis. Not a single one of the 97 fossa ovalis incisions developed silkosis. All of the instances occurred in cases where the operation was performed during the first two-thirds of the year while we were using more buried sutures to close the dead space in thigh and calf wounds. More latterly when we were using only one such suture for every inch length of incision and relying on elastoplast to obliterate the defect no silkosis occurred. Finally, in

*We define silkosis as the condition where buried silk extrudes from and has to be pulled out of an operative wound.

the instances of silkosis, what might be called a dry silkosis was present. In no case was there infection or moistness except within a millimeter of the extruded stitch and at no place did more than one stitch come out. In conclusion, therefore, in our hands infection after operation has played a minor role in varicose vein surgery even though as Freeman (1939) has pointed out "the groin is a susceptible spot for infection." Also, like Freeman, "we have used silk in all of our operations and have had no cause to regret it."

Keloid.—A small nonpainful keloid formed in 1 case.

Hemorrhage.—Hemorrhage occurred in 6 cases, all during the first eight months of the year covered by this report. Four hemorrhages occurred at the fossa ovalis, all in cases done before we adopted transfixion suture of both ends of the main vein. One was in the one patient done in an outpatient office, 1 was in a secondary operation following recurrence, and the other 2 were in simple cases, except that in 1 of them, Case C. S., a lymph gland overlay the saphenous vein. The presence of a lymph gland in this position has, we have found, doubled the difficulty of the operation. The other 2 occurred lower down. One was in our first operation near the knee which was done before we used elastoplast. The other was our first and only attempt to strip the entire saphenous from fossa ovalis to just below the knee on an ambulatory patient. Bleeding occurred high in the thigh above the level of the elastoplast. Two patients had to have the wounds reopened at the fossa ovalis and one at the knee. We believe that following three rules would have prevented all these hemorrhages: (1) Use of transfixion sutures on all main vessel stumps, (2) avoidance of stripping the upper thigh, and (3) the use of elastoplast.

Lymph Drainage.—In our series there were 3 patients with some persistent pain after operation; there were 2 in whom swelling of the leg was a little worse (there was no swelling of the foot or ankle in these cases); and there were several, chiefly those in whom the prescribed course of postoperative injections was never completed, in whom visible but asymptomatic veins persisted. We had no patients in whom the veins seem to be growing larger again. In a few instances spider bursts occurred some weeks after operation.

Our one bad result, however, was in Patient C. S., male, aged 54 years, operated upon June 22, 1940, for veins of eight years' duration, much worse on the right. A bilateral excision and ligation at the fossa ovalis was done and the right leg, previously the worse of the two, was an excellent result. Hemorrhage occurred, however, at the left fossa ovalis; an assistant reopened the wound and ligated a bleeding point. The operation on this side had not been unusual except that a large adherent lymph gland overlay the saphenous vein. Infection occurred which was followed by lymph drainage for three months before the wound finally healed. For a time the lymph secretion was so marked that several hundred cubic centimeters drained off in a day.

Since then the patient has had marked edema and pain in this left, and previously only slightly involved, leg. The edema does not involve the foot but does include the ankle and shin.

VARICOSE ULCERS

The treatment of varicose ulcers is essentially of two types: that directed toward the ulcer and that directed at improving or curing the causative veins. Of methods directed primarily toward the ulcer, the following are to be noted: (1) bed rest and elevation, (2) rubber sponge dressings (the "venous heart" of McPheeters and Merkert, 1931), (3) boots of the Unna or Sooey type,* (4) elastoplast, and (5) ointments, pastes, and powders. Of the latter, sulfanilamide and aspirin are two of the latest. Our own experience has chiefly been with the Sooey boot, elastoplast, and to some extent with sulfanilamide, zinc stearate, and zinc peroxide powders. Wright (1940) used aspirin powder locally and Gould-Hurst (1940) used histamine iontophoresis. Rees (1940) used sulfanilamide powder locally with success. When these conservative means do not work, skin grafting as advised by Linton (1938), Ochsner and Mahorner (1939), and others is to be used, but in our series of the only 3 patients whose ulcers did not heal promptly with other means 1 refused grafting and the other 2 could not be traced.

The other method of treating ulcers is to treat the accompanying veins. This was done in all cases included in this series. Certain men have stated that ligation should not be done in the presence of an ulcer. They advise waiting until the ulcer is healed before proceeding with the ligation. We believe that this is as wise a doctrine as waiting to ligate a bleeding carotid artery until the patient is in condition to stand it. In fact we have ligated veins in cases in which ulcers had persisted as long as twelve years, conservative therapy being administered all this time by the advocates of this doctrine as a preparation for ligation! We believe, therefore, in accordance with Rees (1940) and Luke (1940), Hawkes and Hewson (1940) and many other recent writers that in cases of varicose ulcer ligation should be done to cure the ulcer. Of course, in the presence of acute inflammation, a few weeks' preparative treatment is wise. Furthermore, in ulcer cases, if tests indicate the necessity for multiple ligations down as far as just above the ulcer, only the upper ligations should be done as a first-stage operation. Then later, if and when the ulcer has healed, persistent incompetent veins near it can be ligated or excised.

Hawkes and Hewson (1940) stated in this regard: "It is remarkable to see how quickly the pain will be relieved in an ulcer following ligation. We have seen no untoward complications develop from the

*The Sooey boot which is used at the Henry Ford Hospital, differs from the Unna paste boot chiefly in its phenol content.

ligating of a vein before the ulcer is healed, and we feel that we hasten its closing in doing a ligation and by injecting the feeder veins."

Luke (1940) has ligated 58 cases with ulcers with good results. He believes that temporizing should not be carried too far in these cases and that with surgical treatment "the healing of the long-standing ulcers following this procedure is phenomenal." No ulcer took longer than six weeks to heal, but 3 patients returned with recurrence of the ulcer after initial healing in Luke's series.

In our own series, in 63 patients, ulcers were present in 26. Of 42 patients with a recent follow-up, 22 ulcers were present at the time of operation and of these, 2 were still present at the time of making this report. Of these latter, 1 was an ulcer of nineteen years' duration in which a skin graft was advised and refused, while the other ulcer had healed after operation, but recently had broken down again.

Vitamin B_1.—In 5 cases we used vitamin B_1 by mouth to control pain, usually in the presence of ulcer. In 3 cases there was a good result; in 2 there was slight improvement. The periodicity of the pain in this condition makes this result difficult to interpret. We used 30 mg. of thiamine chloride a day which is equal to the maximum dose used by Ochsner and Smith (1940). These authors and Krieg (1938), the introducer of the method, have been its chief advocates.

SUMMARY

In a series of varicose vein operations personally conducted on 98 extremities of 63 patients during 1940, 217 incisions and 19 strippings were done.

CONCLUSIONS

1. A stereotyped operation should be avoided. The surgical procedure should be individualized to fit the patient and to block all important venous incompetencies as determined by complete diagnostic tests.
2. High ligation and segmental excision of the saphenous vein and all its branches at the fossa ovalis should be performed in all cases submitted to surgery.
3. Additional ligations and excisions lower down on the thigh or leg should be performed as indicated.
4. Stripping gives a better cosmetic result than excision and is preferable to the latter except in cases of superficial, friable, or recently sclerosed veins and for veins high in the thigh.
5. Injection as an adjunct to surgery is best postponed until the second week after operation.
6. Important points in the surgical technique include the use of local anesthetic, silk, transfixion of main vessels, elastoplast bandages, and ambulatory cure in all cases.
7. The one ill effect of consequence in these cases was a slight increase in edema of one leg in two cases and a marked edema in another case.

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CONGENITAL MALFORMATIONS OF THE RECTUM AND ANUS

An Analysis of the Embryological Background, Treatment and Results in 25 Patients

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In 1858 Henry J. Bigelow, Professor of Surgery at the Harvard Medical School, said: "Judging from results, I do not consider the operation for imperforate rectum or even for imperforate anus, a desirable one. I believe that in the present state of the art it is better that a child born with either of these imperfections should die without this operation; although it must occasionally be performed in deference to established opinion."

The scientific and personal criticisms evoked by this honest statement were almost annihilating. More than eighty years have elapsed since that able man voiced his discouraging counsel. The art has carried on, the technique has been improved and the science has forged ahead at a pace that not even he could have foreseen. Even so, eighty years later, surgeons must fear, at least privately, that he might today utter the same statement.

The volume of isolated case reports in the medical literature is tremendous; however, there are few reports presenting any considerable number of cases. This is due to the fact that while not rare, these conditions are uncommon, occurring but once in every 5,000 to 10,000 births. Unfortunately, the great majority of reports have presented individual malformations of the anus or rectum and their immediate or emergency surgical treatment. It is, therefore, difficult to obtain a fair assay of the end results and almost impossible to evaluate specific types of malformations from the prognostic point of view. In short, it is difficult to know just how right Bigelow still may be.

Our series of twenty-five cases is at once discouraging and gratifying. It has extended over a period of years sufficient that a few facts related to therapy and prognosis in certain types of anomalies are beginning to become apparent. It is with this thought in mind that these cases have been reviewed.

EMBRYOLOGY

These congenital malformations of the anus and rectum can be best understood when viewed as perversions of embryological development. There are a great many excellent discussions of this aspect of the problem, among these the comments of Lewis,[1] Arey,[2] Ladd and Gross,[3] and David.[4] Our working concept has been formulated from these sources.

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Normally, the allantois expands to form the primitive bladder, then courses anteriorly to open on the ventral surface of the embryo. The hind-gut is at the level of and posterior to the primitive bladder. Caudad to this region the minute continuation and extremity of the intestinal tract is known as the tail-gut. As early as the third week, the bladder and the hind-gut empty into a common cavity called the cloaca, which is separated from the exterior by the cloacal membrane. In the six-week embryo the urogenital groove is beginning to grow downward and by the seventh week the urogenital and intestinal systems have been partitioned by this groove. The cloacal membrane is then divided into urogenital and anal membranes respectively, and by the eighth week the urogenital membrane breaks down to establish an

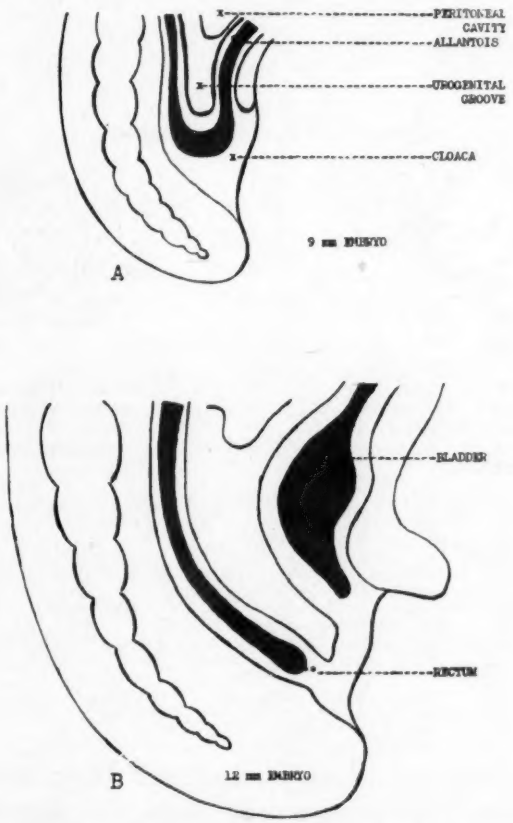


Fig. 1.—*A*. The formation of the cloaca as it exists in the 9 mm. embryo. *B*. The separation of the bladder and rectum in the 12 mm. embryo. (After David.)

external opening. In the region of the future anus an invagination develops which is known as the proctodeum. Normally, the anal membrane ruptures during the eighth week to establish continuity between the proctodeum and the anus. Any failure of the anal membrane to break down results in an imperforate anus.

It is apparent that any arrest in the downward growth of the urogenital groove, which should separate the intestinal tract from the urinary system, will result in residual communicating fistulas (Fig. 1).

The anal sphincters are derived from mesenchyme and are therefore independent in their development from the ectodermal and entodermal origins of the anus, rectum, and intestine. The probable clinical significance of this fact will be considered in the paragraphs on surgical treatment and in the discussion.

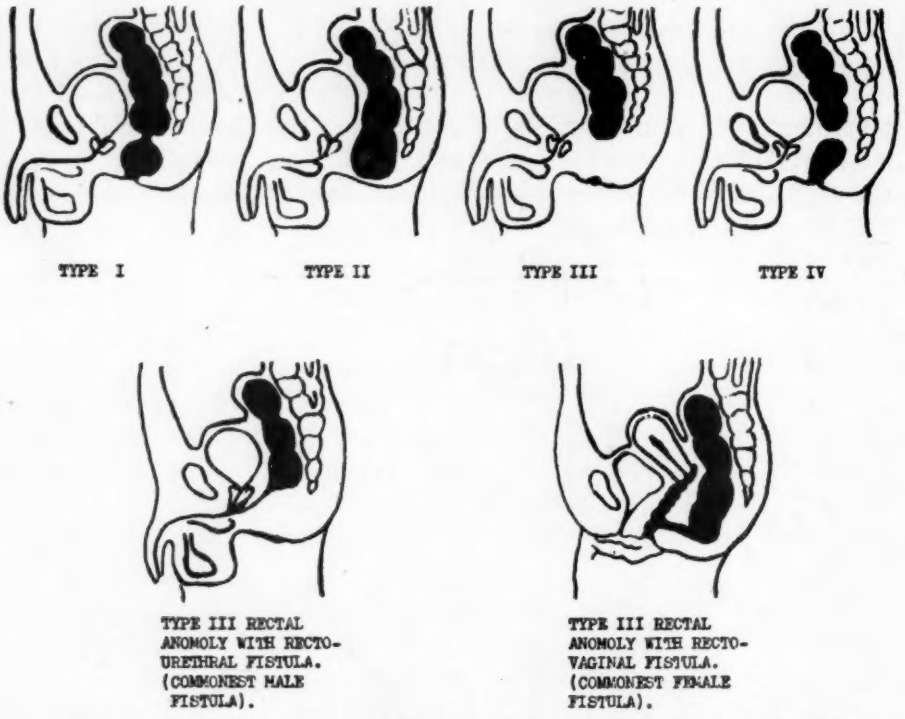

TYPE I
TYPE II
TYPE III
TYPE IV
TYPE III RECTAL ANOMOLY WITH RECTO-URETHRAL FISTULA. (COMMONEST MALE FISTULA).
TYPE III RECTAL ANOMOLY WITH RECTO-VAGINAL FISTULA. (COMMONEST FEMALE FISTULA).

Fig. 2.—A classification of anomalies as arranged by Ladd and Gross. *Type I.* Incomplete rupture of the anal membrane or stenosis from 1 to 4 cm. above the anus. *Type II.* Imperforate anus, patency interrupted by an anal membrane only. *Type III.* Imperforate anus, also an incomplete rectum, the large intestine ending blindly as a pouch within or above the pelvis. *Type IV.* Apparently normal anus and lower rectal pouch but not communicating with a blind overlying rectal pouch. The two blind pouches may be separated by a thin membrane, or considerable tissue may intervene. Any of the above types may occur in males or females, and in either sex the incidence of fistulas is considerable. The commonest type of anomaly in either sex is Type III; the commonest types of fistulas in the two sexes are illustrated above. (After Ladd and Gross.)

CLASSIFICATION

The most logical classification available for the consideration of these malformations has been presented by Ladd and Gross,[3] and more recently reviewed by Berman.[5] Ladd and Gross divide these rectal and anal malformations into four types (Fig. 2). Types I and II are easily explained on the basis of the embryological concepts described above. Types III and IV, where considerable tissue separates the anus from the distal rectal pouch, cannot be due solely to the failure of the anal membrane to rupture. Ladd and Gross suggest that the obliterative process of the tail-gut may abnormally involve the posterior portion of the cloaca and thereby be responsible for considerable defects between the anus and the distal rectal pouch.

The distribution of our twenty-five cases on the basis of this classification is shown in Table I. It will be observed that there are no malformations of Type I. This finding is in sharp contrast to the figures given in the series of Ladd and Gross, who reported that more than 13 per cent of their cases fell into this group. This may be due to the fact that our cases do not include those treated in the out-patient department. In our experience 86 per cent of the entire series was of Type III; this agrees with other reports from the literature.

TABLE I

DISTRIBUTION OF FOUR TYPES OF MALFORMATION OF RECTUM AND ANUS, WITH AND WITHOUT ASSOCIATED FISTULAS

TYPE	MALES	MALES WITH FISTULAS	FEMALES	FEMALES WITH FISTULAS	TOTAL	TOTAL FISTULAS
I						
II	2				2	
III	13	4	4	3	17	7
IV	6				6	
Totals	21	4	4	3	25	7

Fistulas may be associated with any of the four types of anal or rectal defects. The existence of fistulas, as has been pointed out, is explained by a failure to develop a complete septum between the urogenital and intestinal systems by the partitioning downgrowth of the urogenital groove. It is to be expected, then, that fistulas in the male might be either rectovesical or rectourethral in nature; whereas, in the female the fistulas might be rectovesical, rectourethral, rectouterine, or rectovaginal in type. Actually these embryologically anticipated fistulas are found clinically. The rectovesical and rectourethral fistulas in the female are, however, very rare; the explanation apparently lies in the fact that the Müllerian ducts take over existing partition defects in their downward growth. In the female the low rectovaginal fistula and in the male the rectourethral fistula are much more frequently seen than any other types. The common types are shown in Fig. 2.

In the present series fistulas were found only in Type III cases. Seven patients, or 28 per cent, had fistulas. Of these 7 patients, 4 were males and all presented the common rectourethral communications; of the 3 females, all were found to have the low rectovaginal type of fistulas as shown in Fig. 2.

TREATMENT

The treatment of these rectal anomalies is obviously surgical. The extent of this surgical procedure may vary from the inadvertent rupture of a paper-thin rectal or anal membrane, at the time of the postnatal rectal examination, to the most complex reconstructive procedure superimposed upon an original colostomy.

It is not our purpose to discuss in detail all of the surgical procedures that may be useful in dealing with these malformations. Certain general principles, however, may be useful to the experienced surgeon in adapting his individual procedure to his specific problem; further suggestions are to be found in the excellent discussions of David,[4] Berman,[5] and Chandler.[6]

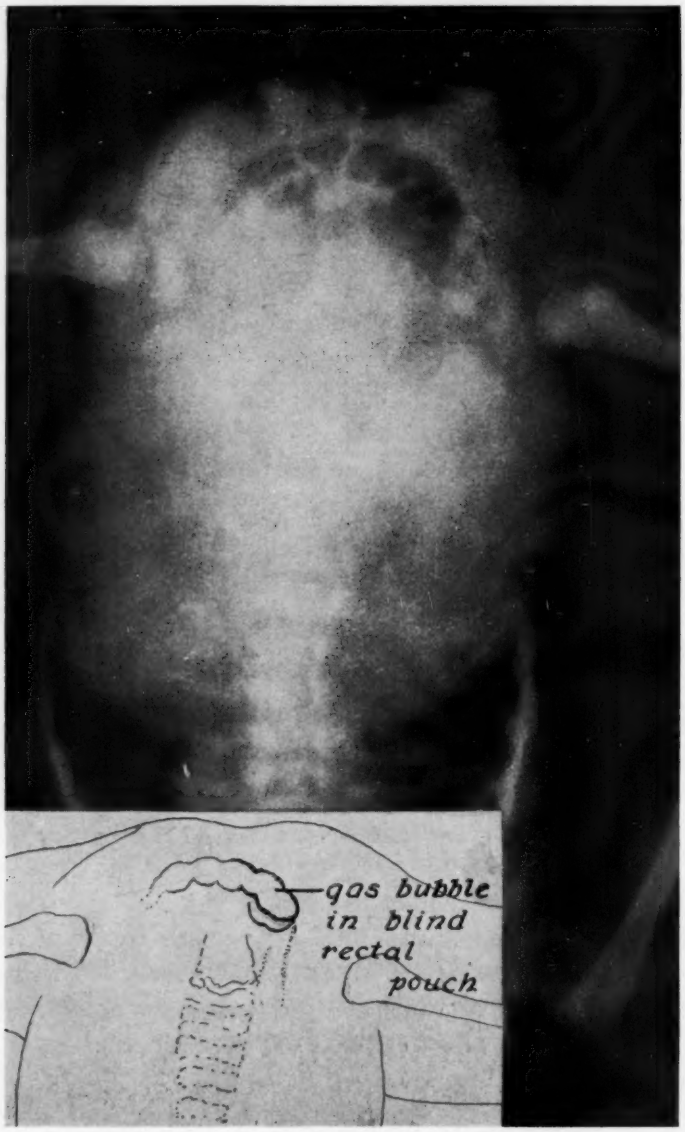


Fig. 3.—X-ray shadow outlining the gas-filled blind pouch of the incomplete rectum. To obtain this contrast the child is held in the inverted position.

In Types II and IV where there persists but a thin anal or rectal diaphragm, the obstructions may be adequately relieved by simple longitudinal incision or by perforation with a hemostat. The last patient in

the present series was adequately relieved by the nurse in the admitting office when she took the routine admission temperature with a rectal thermometer.

In those patients with Types III and IV, where more tissue than a membranous diaphragm separates the anal area or pouch from the blind end of the rectum, a simple incision or direct perforation may be hazardous. In these it becomes essential to obtain a precise idea of the position of the rectal pouch. This can be determined by clinical and roentgenologic examinations. As the child cries or strains there may be no bulging of the perineum when the pouch lies high in the pelvis, but if the defect is not great, the surgeon may obtain a fairly accurate impression of the position by means of palpation alone. It is, however, unnecessary to guess about the position of the high-lying rectum for by the method of Wangensteen[7] an accurate localization can be made. Due to the fact that gas appears in the large intestine within twenty-four hours after birth, and will seek the distal blind rectal pouch when the child is held in the inverted position, the rectum can be clearly visualized with the x-ray by means of the fluoroscope or a roentgenogram. It may be expedient to mark the anal region with a coin or other suitable radiopaque object. (Fig. 3.)

Having determined the position of the end-gut, the surgical reconstruction is relatively simple. By making a longitudinal incision in the raphe, bleeding is held at a minimum. In view of our opinion that sphincter muscles exist in most if not all of these cases, it will readily be appreciated why we are anxious to cut through the muscle-bearing area in but one place. This can be most conveniently done by beginning the incision well anterior to the anal dimple and carrying it posteriorly into but not through the dimple and therefore the sphincteric ring. In this way we hope to cut only the anterior fibers. With the incision so placed, the problem of finding the rectum should not be great if the position has been accurately determined preoperatively by the above methods. The pouch is then freed from the surrounding tissue and brought down to the cutaneous margins where it is opened and then anchored with interrupted sutures. The perineal body is adequately restored by bringing the levator ani muscles together in front of the rectum with catgut sutures. The procedure described here is similar to that illustrated in Fig. 5 *B*. As the meconium is sterile, the danger of infection is minimal.

Following operation a tendency toward stenosis exists and, therefore, postoperative dilatation must be carried out faithfully. In some cases it has been necessary to dilate the rectum and anus first daily for weeks and later weekly for years. Fig. 4 presents a series of photographs of a patient who serves as an example of this problem. *A* was taken when the infant was 12 hours old, and before the operation had been performed. *B* was taken three days after the operation, when the infant

was 4 days old. *C* shows the same patient four years later with a perfectly functioning anus although it is somewhat distorted by scar tissue. At the time of *C* the patient required dilatation once a month. These photographs illustrate a coexistent pseudohermaphroditism with the penis curled forward so as to resemble a clitoris. The bifid, labialike scrotum contained two apparently normal testes. This situation has been recently relieved by means of reconstructive procedures.

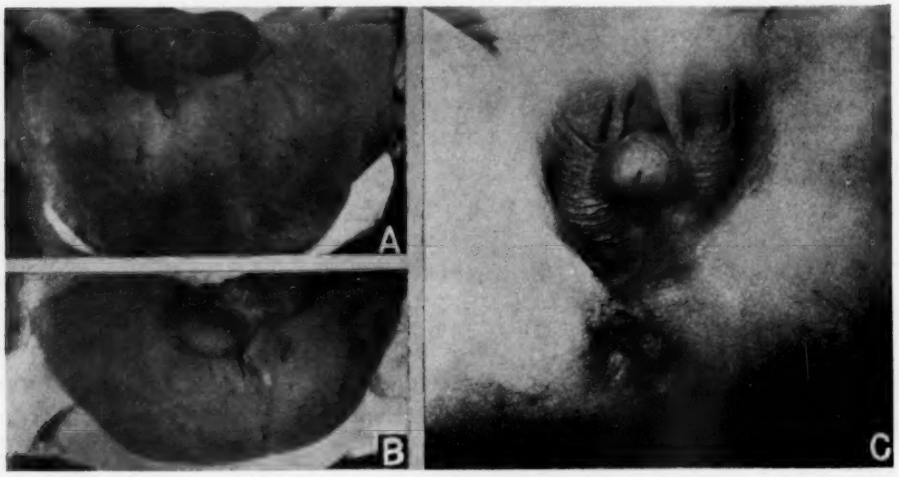
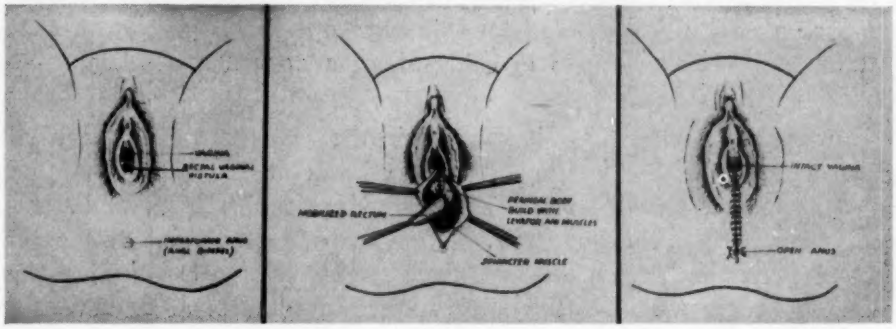


Fig. 4.—*A*. An infant 12 hours old with an anal dimple which is imperforate. *B*. Four days later, after an incision carried halfway through the dimple was made deep enough to extend into the overlying rectal pouch. *C*. The same child four years later with an open rectum and anus and a perfectly functioning anal sphincter.

The surgical supervision of these congenital anomalies varies but little in the presence of rectourethral or even rectovesical fistulas. In my own experience as has been pointed out above, the fistulas were all of the urethral variety. A case in point, with a rectourethral fistula associated with a Type III malformation, has proved particularly instructive. This patient, now 8 years old, had a colostomy performed immediately after birth, at another hospital; he was later transferred to this service. When he was 4 years old the colostomy was closed and a perineal opening was established. Postoperatively a rectourethral fistula became apparent because of a fecal urethral discharge. In addition to this complicating fistula there was a severe rectal stenosis. The severity of a stenosis generally corresponds, more or less, with the extent of the defect. In this patient the distal rectal pouch lay at the level of the pelvic inlet, so that the defect was considerable. The ordeal of frequent dilatation of the rectum, rather than the complicating fistula, was responsible for the eventual decision of the family to submit the child for further surgical treatment.

After a prolonged period of colonic irrigation the child was considered ready for operation. The urethra and rectourethral fistula were injected with an aqueous solution of methylene blue, immediately before

the operation, the catheter being left in the bladder. Prepared in this manner, the child was taken to the operating room where through a longitudinal incision in the perineum, carried posteriorly into the rectum and anus, it was possible to expose the fistulous tract in its entire extent, which was then completely excised; the urethral end being loosely closed over the indwelling catheter. The rectal opening of the tract marked the lowest point of what appeared to be normal-looking rectal mucosa, so the tract and all of the stenotic, scarred, and tortuous terminal rectum was excised. The mobilization of the suprajacent normal rectal tissue was then quite simple and the mobilized segment was easily brought down to the cutaneous margins of the anus. This procedure served to excise the fistula, cover the fistulous site, and relieve the stenosis. During this reconstructive operation no evidence of sphincter muscle was found; therefore, it seems unlikely that rectal continence will develop. Since this operation, the patient has for the first time, however, shown some control. This control appears, however, to be a matter of gluteal rather than sphincteric action, so the operation may be regarded as a therapeutic failure. From the point of view of his rectal stenosis and rectourethral fistula, however, his treatment should be regarded as quite successful.



A. *B.* *C.*

Fig. 5.—The operation used for the repair of the Type III (female) rectal anomaly associated with a rectovaginal fistula. *A.* The perineal view of such a fistula and the imperforate anus. *B.* The incision, the excision of the fistula, the mobilization of the rectum, and the reconstruction of the perineal body with the levator ani muscles. *C.* The completed plastic procedure; the vagina has been reconstructed, the perineum closed, and the anus has been built in the site of the imperforate dimple. The sphincter has been divided at one point to avoid destruction of the muscle.

The only fistulas seen by us in females were of the low vaginal variety. In these patients, as is often the case, the fistula was of sufficiently large caliber to permit the evacuation of feces during infancy. The operations were performed at ages of 7, 8, and 3 years, respectively. This combination of rectovaginal fistulas and the Type III anomaly is illustrated in Fig. 2.

The three sketches of Fig. 5 present our method of treating the imperforate anus of Type III in which there exists a low rectovaginal fistula. The incision is carried from the fistula posteriorly in the raphe

into, but not through, the anal dimple. The rectum and fistula are readily exposed in this way and may be completely mobilized. However, the opened free end of the fistulous tract has been found to be unsuitable for the reconstructive procedure and should be cut away. The free rectal pouch can then be brought down to the cutaneous margins of the anal dimple and anchored there with interrupted, radial sutures. This gives a complete rectovaginal septum and the perineal body can be constructed by bringing together the two levator ani muscles, with catgut sutures, in front of the rectum. In the three cases this operation has proved satisfactory from the point of view of rectal and anal patency as well as sphincteric control.

It is interesting to note that Diffenbach, of Vienna,[8] performed an operation similar in all essential respects to the one outlined above as early as 1826.

DISCUSSION

From my comments on the surgical treatment of these patients it will be noted that the importance of the perineal approach is emphasized. By means of digital and roentgenologic examinations that have been described, it is possible, I believe, to localize the blind end of the rectum with mathematical precision. The physiologic and psychologic advantages of a normally placed distal intestinal opening not only warrant but dictate heroic measures to bring about a normal anatomical relationship of the parts.

Numerous comments have been made in the past about the congenital absence of anal sphincters. As has been pointed out in the above section on embryology, the sphincter muscles arise from mesodermal components; whereas, the anus and rectum are of ectodermal and entodermal derivation. This thought alone might lead us to question the accepted order; namely, that anal and rectal defects are frequently associated with the absence of the sphincter. To be certain, it is comforting in the face of the tragedy of rectal incontinence to feel that there was a preoperative and congenital absence of sphincters. Yet careful consideration of such cases may, and often does, reveal other adequate reasons for this incontinence. In other rectal surgery we are loath to incise the sphincter muscles at more than one point lest damage to those muscles result, yet in the surgery of the absent rectum or anus such care is not stressed. It is, then, perhaps fair to ascribe some of these misfortunes to destructive surgery. In my own experience, the instances of persistent incontinence have occurred in cases where the postnatal procedure was a colostomy and in which the perineal opening was established years later. This suggests the possibility of the atrophy of disuse in the sphincter muscles.

It is difficult to support by direct testimony the belief that sphincter muscles are present in the vast majority of these cases. In a consider-

able proportion of patients the presence of a completely adequate sphincter is amply demonstrated by clinical examination and functional test; these, however, are not the cases in point. The instances that have given rise to this controversy are generally of Type III, where there is an anal dimple and a considerable underlying defect. In these patients palpation, though unsatisfactory, leads one to expect no subjacent muscle. This was precisely the clinical picture that was presented by a recent patient on our service. The infant had had a colostomy performed in another hospital because the surgeon in that institution had felt that there was no clinical evidence of an anal sphincter beneath the anal dimple. This infant died shortly after admission. Fig. 6 shows the anteroposterior and lateral x-ray views after instillation of barium solution into the colostomy. The radiopaque mixture is seen coursing through the rectourethral fistula into the urethra and up into

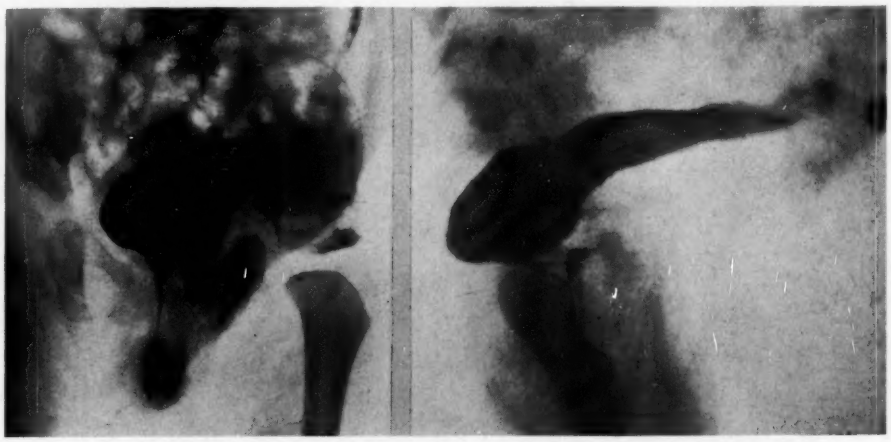


Fig. 6.—Anteroposterior and lateral x-ray shadows demonstrating a Type III anomaly combined with a rectourethral fistula. This opaque solution was introduced through a colostomy opening and has outlined the rectal pouch, rectourethral fistula, and the urethra.

the bladder. Fig. 7 depicts the necropsy specimen taken from the same patient. The rectal pouch, fistulous tract, bladder and urethra, and the perineum have been removed intact, and then exactly hemisected. This gives a pathologic specimen which demonstrates precisely the anomaly illustrated by the male fistula diagram in Fig. 2. Careful dissection failed to demonstrate any perianal muscle tissue, but the existence of a sphincter was established by means of the microscope (Fig. 8).

Finally, it must be said in this discussion of the congenital absence of anal sphincters that our clinical impression is that most, if not all, of these patients are normally equipped with anal sphincters. Our embryological and histological evidence would seem to support this clinical observation.

The various surgical procedures have been briefly reviewed. Depending upon the type of the malformation, these patients fall into two

groups. The first group of patients requires emergency surgery because of the obstruction; those in the second group have fistulous tracts that permit the postponement of operation.

In those requiring emergency treatment because of obstruction it would seem preferable to consider the emergency as one demanding surgical intervention within the first few days, but not necessarily within the first few hours, of life. This simple concept might eliminate

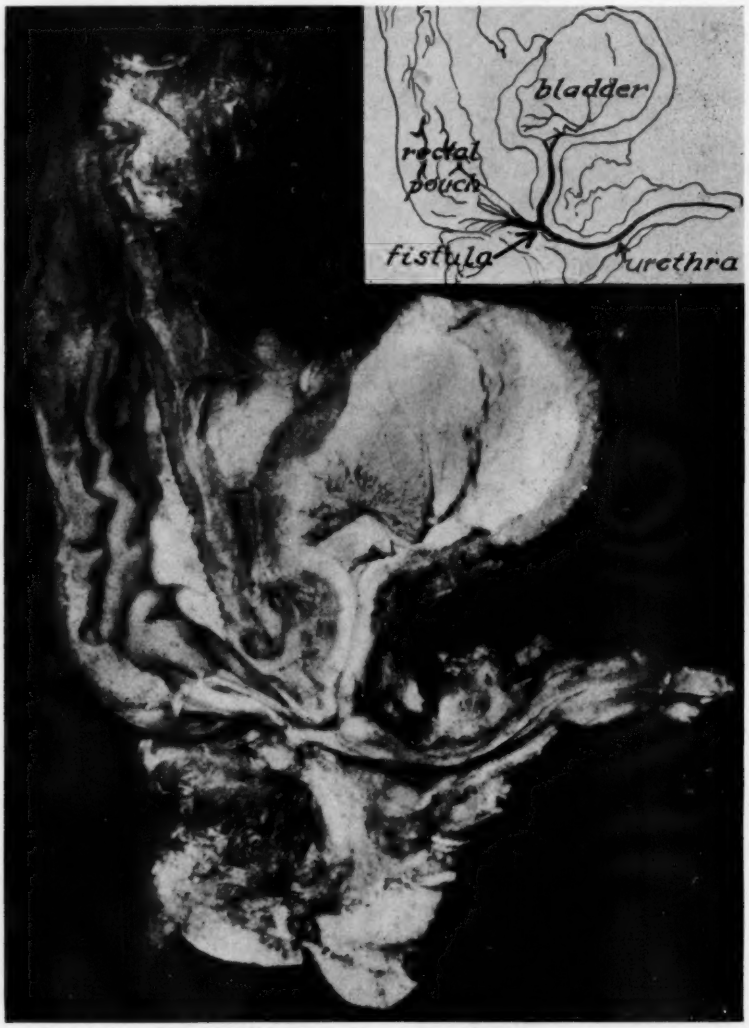


Fig. 7.—Post-mortem specimen of the patient studied in Fig. 6. The pelvic organs have been removed intact and hemisected. The bladder, urethra, rectal pouch, recto-urethral fistula, and rectal defect are demonstrated.

the casualties incident to surgical intervention in the home and it might obtain for the patients more complete examination in the hospital and more deliberate surgical consideration.

The second group, those who can have their reconstructive operations performed as elective measures, are, on the whole, a more satisfactory

group. In our series of cases this group was made up of but 3 patients; these were all of Type III in females with low rectovaginal fistulas as illustrated in Fig. 2. Many surgeons have advocated waiting for the reconstruction until these children are from 6 to 8 years old, when the structures are larger and more substantial; we have done so twice. However, in our last patient the reconstruction operation demonstrated in Fig. 5 proved eminently satisfactory at the age of 3 years. From this limited experience we are convinced that there is no real advantage in waiting more than two or three years and we also feel that the possibility of atrophy in a nonfunctioning anal sphincter may, in itself, prompt the earlier operation.

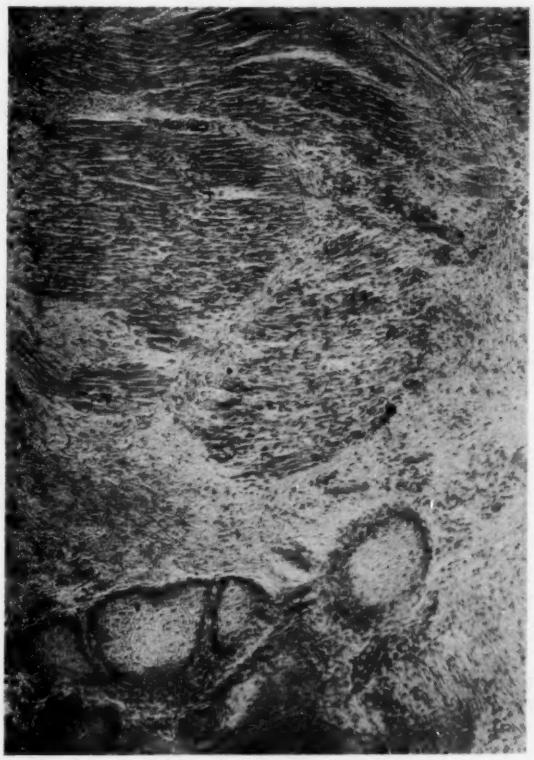


Fig. 8.—Photomicrograph demonstrating perianal muscle tissue lying immediately above subcutaneous glands. This is interpreted as sphincter muscle.

When possible, it is well to attempt the suture of the divided sphincter after anchoring the rectum in the newly formed anus. The importance of dividing the sphincter at but a single point has been stressed often in considerations of rectal surgery in general; we feel that this sound principle is no less significant in the treatment of these congenital malformations.

ANALYSIS OF CASES

In a series of 25 cases, 10 patients, or 40 per cent, have lived. Seven of these are regarded as having satisfactory results, due to the fact that

all fistulas are closed and that all of the patients have rectal control. Three of the results are regarded as unsatisfactory due to rectal incontinence.

Of the 15 deaths, 5 must be regarded as surgical, although 1 infant was brought to the hospital in a terminal condition following an incomplete and unsuccessful perineal operation in the home by the family physician.

The 4 other infants died in the hospital; 2 were found to have multiple congenital anomalies, 1 developed bronchopneumonia, and the fourth died of hemorrhagic disease of the newborn.

The 6 remaining patients who eventually died were all discharged from the hospital in good condition but died within five months. Two of these died from undetermined causes; 1 two weeks and the other five months after discharge. The third patient was discharged in good condition but returned a few days later and died on admission; as no necropsy was obtained the cause of death was not conclusively established. The fourth infant expired with laryngotracheal bronchitis five months after leaving the hospital. Approximately one year after discharge the fifth patient died in another hospital following the surgical correction of a rectourethral fistula. The last patient died from hemorrhage following dilatation of the rectum in the home.

SUMMARY

1. Twenty-five cases of malformation of the rectum and anus have been reviewed.

2. These malformations represent arrests and perversions in embryological development.

3. Of this series of patients, 21, or 84 per cent, were found in males; 4, or 16 per cent, were found in females. Seven of the males had associated rectourethral fistulas; 3 of the females had associated rectovaginal fistulas.

4. The surgical measures most useful in the treatment of these conditions have been briefly reviewed.

5. The most satisfactory therapeutic results may be expected in those patients having only a thin obstructing diaphragm and in the females with large rectovaginal fistulas that allow postponement of the operation until the patient is from 1 to 3 years old.

6. The clinical impression that most, if not all, of these patients have normal anal sphincters would seem to be supported by embryological and histological evidence.

7. Ten of the 25 patients, or 40 per cent, are still living. Seven of the 25 patients, or 28 per cent (7 of the 10 living patients, or 70 per cent), are regarded as clinical cures and have good rectal control.

8. These patients suffer a high nonsurgical mortality, partially due to the high incidence of associated congenital anomalies.

9. Physiologic and psychologic factors justify heroic measures to establish the normal anatomical relationships in malformations of the rectum and anus.

The author is greatly indebted to Dr. Fenwick Beekman, Director of the Children's Surgical Service of Bellevue Hospital, for his thoughtful counsel and guidance in the study of this subject and these patients. The cooperation and suggestions of Dr. Douglas Symmers, Director of Laboratories, Department of Hospitals, New York City, in the preparation of the pathologic studies, and the preparation of the embryological discussion by Dr. George Husser, University of California Hospital, San Francisco, Calif., are also very much appreciated.

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BONE TUMORS WITH REFERENCE TO THEIR TREATMENT*

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IN APPRAISING any method of therapy it is necessary to know the essential pathology, the natural history of the disease, and what influence specific therapy may have upon it. The classification of bone tumors based upon the relation of bone development and subsequent tumor formation separates the tumors into specific types, each of which follows a definite course. A survey of these groups reveals more accurately the effect of treatment, and prognosis is thus placed upon a sound basis.

CLASSIFICATION

I. Tumors derived from precartilaginous connective tissue
   a. Osteochondroma
   b. Chondroma
   c. Primary chondromyxosarcoma
   d. Secondary chondromyxosarcoma
   e. Osteoblastic osteogenic sarcoma

II. Tumors related to subsequent cartilaginous growth
   a. Bone cyst
   b. Benign giant cell tumor
   c. Chondroblastic sarcoma
   d. Osteolytic osteogenic sarcoma

III. Certain tumors of nonosseous origin intimately connected with the bone
   a. Ewing's sarcoma
   b. Multiple myeloma
   c. Fibrosarcoma
   d. Metastatic carcinoma
   e. Angioma
   f. Recurrent myositis ossificans
   g. Hand-Schüller-Christian's disease

For a full description of the types of tumors, one is referred to previous publications.[1-3] It is the purpose of this communication to emphasize the treatment best suited for the tumor. A brief survey will be given of each group, the treatment used, and where irradiation seemed of benefit, the physical agent used. No comprehensive rule can be laid down as to whether a tumor process is radiosensitive. Experience has been our best teacher as to the behavior of tumors under radiation. A bitter lesson has been learned in that radiosensitivity does not parallel radiocurability. The term, radiosensitivity, is a relative one. A shift in the technique of giving the physical agent, either x-rays or radium, frequently reveals a change in the response of the tumor to the agent.

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I. TUMORS DERIVED FROM PRECARTILAGINOUS CONNECTIVE TISSUE

It may be said in general that tumors of this group are not radiosensitive, while isolated examples may be pointed out in which the growth of the tumor has been affected by irradiation, or where the x-rays and gamma rays have been used successfully as an adjunct to surgery.

Osteoma or osteochondroma is primarily a surgical problem when treatment is necessary. This is the largest group of benign tumors arising from precartilaginous connective tissue in the skeleton.[4-6]

These neoplasms are most frequent near the ends of the long bones of patients between the ages of 10 and 25 years. The distinctive diagnostic features are the pedicle of normal bone protruding from the bone cortex and the rim of cartilage overlaying it. A similar structure may be seen microscopically. In the x-ray picture is depicted the compact differentiated outgrowth of bone and an overlaying cartilaginous cap flecked with calcium. Cases of single osteochondromas without symptoms frequently go unnoticed. They may be left untreated but should be watched by interval x-ray examinations, since they may undergo secondary malignant change, particularly after the age of 30 years. Histogenetically, an exostosis represents a failure in the accurate approximation of tendon and cortex, with proliferation of cartilage from the tendon and protrusion of proliferating cortex. Simple excision usually suffices to cure those osteochondromas which produce pain or dysfunction.

In the hereditary or multiple exostoses[1, 7, 8] treatment is more difficult. The regions most frequently and severely affected are those of the forearm and foreleg, the bones of which may be fused at one point. The prognosis as far as life is concerned is good, but there is no adequate form of treatment except operation for correction of deformities as in single osteochondroma. In a few cases with multiple skeletal involvement, I have observed secondary malignant change in the cartilaginous growths resulting in death from chondromyxosarcoma. X-ray or radium therapy plays little role in the treatment of these cases.

Chondroma is a common type of cartilaginous tumor often classified with the benign exostoses.[1, 9] It occurs in the small bones of the hands and feet, also in the spine, ribs, and sternum. In the small pipe bones it appears as a central lesion with rarefaction, visible in the roentgenogram as a cystic area, within a shell of cortical bone. It is rarely multiple and rarely affects long bones. In deciding whether a particular chondroma is to be treated from the benign or malignant standpoint, the location and not the pathologic changes must be given primary consideration. Chondromas in the small bones of the hands and feet are to be looked upon as benign lesions curable by thorough extirpation (curetting and cauterization). True chondromas of large size occurring about the sternum or spine or in the long bones must be looked upon as potentially malignant. They should be removed if possible. X-ray

or teleradium therapy has been of benefit in retarding the growth in four cases. One patient survived eighteen years after diagnosis, with repeated series of x-ray treatments.

Primary chondromyxosarcoma is a form of periosteal osteogenic sarcoma.[1, 10] It arises primarily in young patients (aged 14 to 21 years) and at the sites where tendons insert directly into the bone. The favorite sites are about the knee, in the lower femur or upper tibia, also at the shoulder and pelvic girdles. The neoplasm is composed of tumor cartilage, some ossification, and areas of cystic destruction (Fig. 1, *A* and *B*). In the x-ray it appears as a subperiosteal shadow streaked with calcium spicules. It does not involve the cortex until late in the disease, causing bone destruction. Permanent cures in this group average 9 per cent. Three of five cases surviving five years or more received irradiation in conjunction with amputation. All surviving patients had amputation performed, suggesting irradiation had little or no influence on the results. Irradiation, however, relieved pain in many instances and reduced soft part swelling.

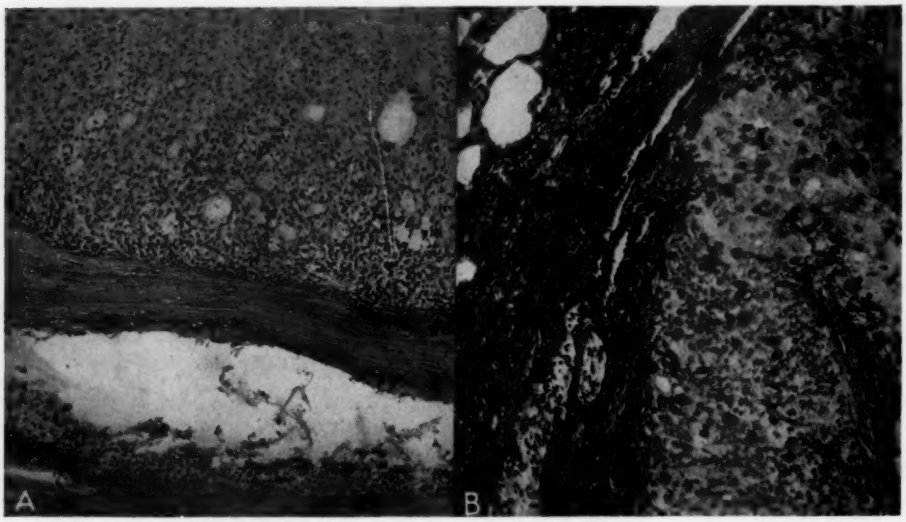

Fig. 1.—Photomicrographs of primary chondrosarcoma showing *A*, proliferation of embryonic connective tissue with the formation of hyaline matrix containing many fetal, cartilage cells; *B*, fully developed tumor cartilage cells with areas of fetal myxomatous tissue. This tumor is highly radioresistant.

Secondary chondrosarcoma is a malignant tumor arising on the basis of a pre-existing chondroma or osteochondroma, occasionally complicating Paget's disease or hereditary chondrodysplasia.[1, 11, 12] Most of the patients are between the ages of 35 and 55 years. The locations of the tumor show a tendency for the regions about the upper humerus, ribs, femur, and heel to be involved.

In the x-ray picture it is most easily diagnosed where a portion of the primary lesion still remains and where the superimposed malignant

change appears as a fuzzy infiltrating periosteal shadow flecked with calcium. Destruction of the cortical bone follows, occasionally with pathologic fracture.

Microscopically, the tumor is composed of cartilage, large amounts of myxomatous tissue, calcified cartilage, and proliferating connective tissue elements. The age of onset is much later than in primary chondrosarcoma, usually over the age of 25 years. The upper humerus, ribs, and heel are frequent sites of origin. Of 18 cases (26 per cent) surviving five years or more up to 1935, 6 patients received irradiation: 2 in combination with curettement only and 4 with resection only. In 4 cases with resection and no irradiation the patients have survived five years or longer. Eight cases had primary amputation. It would seem, therefore, that while irradiation may be of benefit as an adjunct to surgery, the relative benignity of the lesion plays a more important role in the cure of the tumor process.

Osteoblastic Osteogenic Sarcoma.—This is the most highly differentiated type of osteogenic sarcoma.[1, 2, 12, 13] Fibrous elements may predominate microscopically, but usually proliferation of osteoblasts and new bone formation are seen, with rare islands of cartilage. This tumor is most frequent between the ages of 15 and 25 years and is usually situated in either the lower end of the femur or the upper end of the tibia. Other locations are the upper humerus, ribs, vertebrae, and pelvis.

The x-ray picture is characterized by dense, radiating, new bone in the periosteal zone, giving a "sun-ray" appearance. Later the medullary cavity is obliterated by tumor bone with some secondary destruction of the cortex. Histologically, the tumor is composed of large osteoblasts with a conglomerate scattering of osteoid substance (Fig. 2). Cures have been achieved in 26 per cent of the cases. Of 18 patients surviving five years, 5 received irradiation as an adjunct to surgery (largely amputation). In 1 individual, with a lesion in the lower femur, following exploration and chiseling away of the tumor, the area was exposed to the radium pack. Later the leg was amputated. This patient survived twelve years after the amputation. This result again may be attributed to cell differentiation with some natural restraint factor present.

From this study it becomes increasingly clear that the cell differentiation of the tumor process plays an important role in the prognosis and in addition, that radical extirpation is the procedure of choice.

II. TUMORS RELATED TO SUBSEQUENT CARTILAGINOUS GROWTH

Bone Cyst.[1, 14, 28]—The benign solitary bone cyst is frequent in children under the age of 18 years. It usually occurs in the shaft near the upper ends of the humerus, femur, or tibia and runs a protracted and benign course. Pathologic fracture is the only acute phase of the disease

and probably the most frequent reason for consulting a physician. The x-ray picture shows a central expanded bone defect, symmetrical and regular in contour.

Microscopically, a healing bone reaction is noted about the cavity which may be lined by fibrous tissue. It usually is filled with straw-colored fluid or remains of old hemorrhage. Some cysts are trabeculated.

Spontaneous arrest of the lesion without obliteration of the cavity results in the latent bone cyst. Fracture through the cyst usually results in healing.

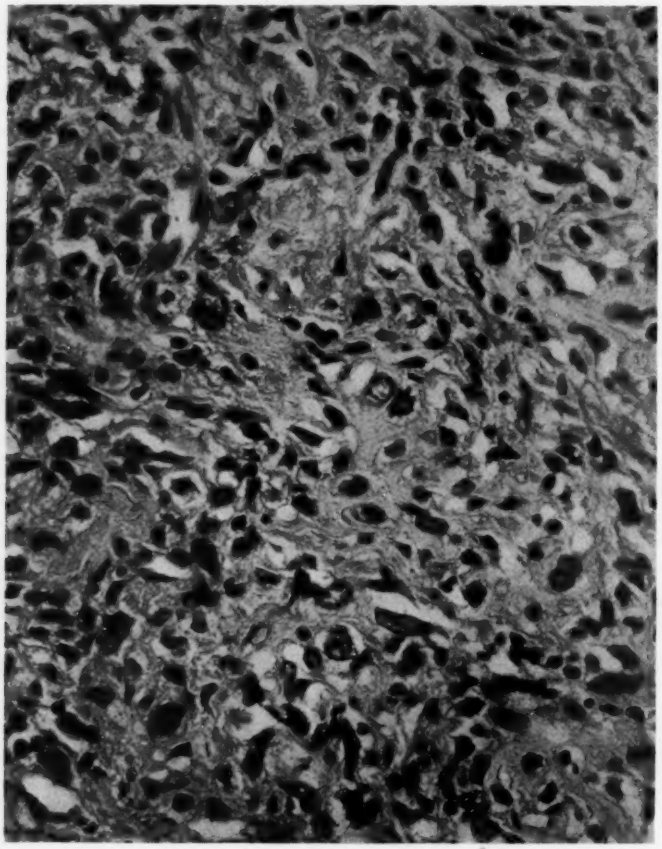

Fig. 2.—Photomicrograph showing large tumor osteoblasts and the osteoid intercellular substance typical of sclerosing osteogenic sarcoma. This tumor is radioresistant.

Variations of the simple bone cyst may be encountered:

1. *Giant-cell variant* of the bone cyst[1, 15] in which the duration of symptoms is found to be shorter; located invariably near the epiphysis of the bone on the metaphyseal side. It is most commonly found in the greater trochanter of the femur and lower radius. In the x-ray it is polycystic in character, more subcortical than central, and most frequently trabeculated.

Microscopically, the walls are lined by fibrous stroma containing variable numbers of giant cells. Hemorrhage is common. These lesions stand midway between the typical bone cyst and giant-cell tumor.

2. *Polycystic osteitis fibrosa,*[1, 2] a multilocular structure occurring either as a single lesion or with generalized osteitis fibrosa cystica. The cysts also occur near the epiphysis on the metaphyseal side, but extend over a considerable area of the bone shaft. The duration of symptoms averages about five months. In the x-ray they appear as an aggregation of small cysts, which have more or less coalesced, giving a polycystic appearance with some expansion of the cortex.

Histologically, there are many small cysts, usually filled with blood and surrounded by giant cells. Varying amounts of fibrous tissue may be seen.

3. *Multiple osteitis fibrosa cystica,* a generalized demineralization of bones due to hyperparathyroidism.[1, 16, 17] Rarefaction of bone, bending deformities, cystic tumor areas, and fractures are noted. Bone involvement is most pronounced in the pelvis, spine, and long bones. The microscopic picture may show typical giant-cell tumor or healing bone reaction, depending on the activity of the disease.

The prognosis as to life is good in all forms of bone cysts and osteitis fibrosa.

In the solitary bone cyst of the adult in which symptoms are absent, no treatment is indicated.

In the solitary bone cyst of young people, where fracture has occurred and the position of the fragments is satisfactory, simple fixation gives a good result.

If the lesion is progressive after several months, exploration and curettement, followed by chemical cauterization, is indicated. Bone chips or crushing of the bone shell may be used to obliterate the cavity.

In the acute bone cyst (giant-cell variant) moderate amounts of x-ray therapy given in divided doses[29] is considered adequate treatment. Should irradiation fail, operative interference may be necessary. Primary curettement and cauterization yield excellent results. Irradiation followed by surgical procedures gives less satisfactory healing in the aggressive bone cysts.

In multiple osteitis fibrosa the possibility of parathyroid tumor must be ruled out, and if suspected, the region of the glands should be explored surgically or irradiated.[18, 19] A diet rich in calcium, phosphorus, and vitamin D is a necessary adjunct to the therapy.

Benign Giant-Cell Tumor.[1, 20]—An epiphyseal lesion occurring after the age of 18 years. It is most frequent in the lower end of the femur, upper end of the tibia, and lower end of the radius.

The duration of symptoms averages fourteen months. The sequence of events is trauma, pain, tumor, and occasionally pathologic fracture. In the x-rays an early giant-cell tumor shows a defect situated asymmetrically in an epiphysis. The defect is surrounded by a bone shell which may be perforated. The lesion is progressive and in a few instances may show sarcomatous degeneration.

Microscopically, the tumor is composed of large multinucleated giant cells, embedded in a mass of small round cells. The giant cells average

over 30 per low-power field and the number of nuclei per cell varies from 15 to 200. The giant cells are more numerous about hemorrhage, spicules of old bone, or small cystic areas (Fig. 3). There are a number of variants of giant-cell tumor. Certain lesions of sesamoid bones and in the jaw about the teeth are related pathologically to giant-cell tumor.

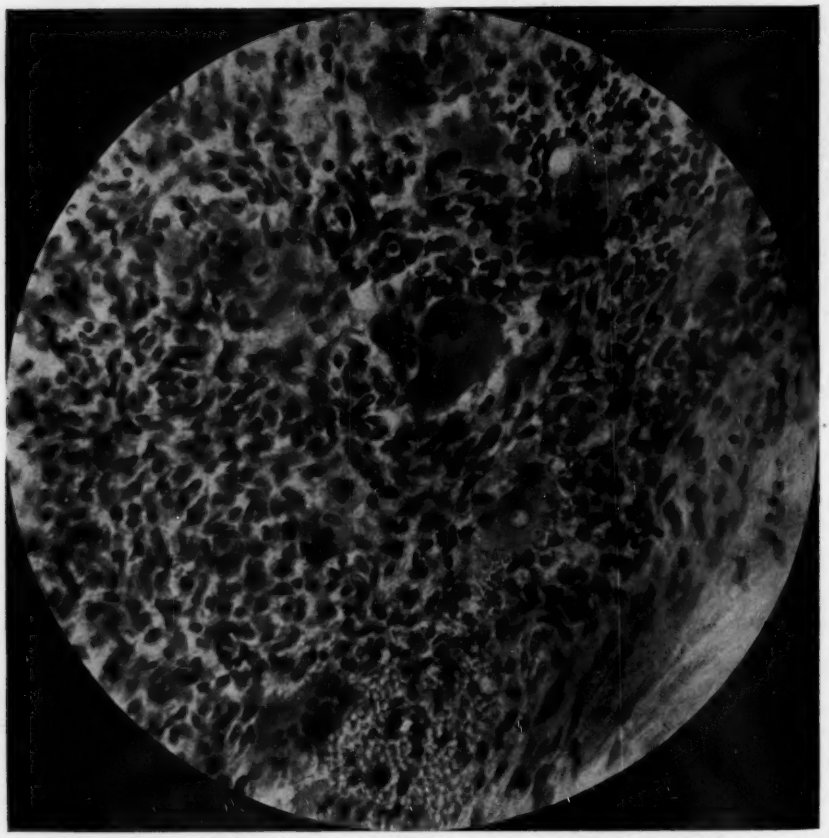

Fig. 3.—Photomicrograph of giant-cell tumor. Giant cells are embedded in a stroma of small round cells and spindle cells. Many small blood vessels are present. Damage to these capillaries represents a factor in the radiosensitivity of this tumor.

Perhaps 85 per cent of giant-cell tumors can be accurately diagnosed on the history, physical examination, and roentgenographic studies. There is increasing evidence, however, that a definite percentage will show malignant degeneration.[21, 22, 25] Because of this fact, any doubtful or atypical case must be biopsied, followed by thorough curettement and cauterization if benign, or by such radical procedure as may be indicated if malignant.

Conservatism in the treatment of giant-cell tumor has been increasing since 1912.[23, 24] If one has to consider the economy of time, surgery is the procedure of choice.[26, 27] In a primary case, not too advanced, curettement followed by cauterization is advocated, especially in the lower femur and the upper tibia. In advanced lesions of the ulna, fibula,

or radius, resection or irradiation may be used. Recurrences may be troublesome and call for further curettement or even resection where possible. They are usually due to incomplete removal, perforation of the bone shell, or declining reaction of the cortex due to age.

Many giant-cell tumors are radiosensitive, but the mechanism of response is not well understoood.[30] Opinion varies greatly on the efficacy of irradiation versus surgical intervention in benign giant-cell tumor. It is well established that certain lesions irradiated alone or treated by surgery alone heal perfectly, but the combination of the two is not advocated. Many unfortunate results have accrued from such combination of therapy.

Results by irradiation are less favorable in the weight-bearing bones.[31] Suberythema doses of irradiation, given with sufficient intervals of time, are an important factor in avoiding deformity and other complications.

There are many giant-cell tumors which are inoperable because of their location or extent of the disease and in which x-ray therapy will adequately control the process.

Irradiation should be given sparingly near an epiphysis of a growing bone.

Pre- and postoperative x-ray therapy have little place in the treatment of giant-cell tumor.

Chondroblastic Sarcoma.—This is a rare osteolytic variant of osteogenic sarcoma, sometimes erroneously called cartilaginous giant-cell tumor.[1, 32] It arises from a proliferation of cartilage, at the epiphyseal line, during the age of puberty. It may be seen about the upper end of tibia, lower end of femur, and upper end of humerus. The duration of symptoms prior to operation averages five months.

In the x-ray picture there is a characteristic mottled cystic area of bone destruction, with expansion of the bone shell and usually some periosteal reaction. Not infrequently the tumor bears a marked similarity to giant-cell tumor.

Microscopically, one sees masses of young and adult cartilage undergoing calcification, with areas of uncalcified matrix. The tumor is extremely vascular. Near the vascular areas and about the periphery of the cartilage numerous giant-cell osteoblasts are seen (Fig. 4). Many of these tumors are quite malignant, but irradiation has been a most effective method of treatment in many of the patients who have survived. In fact, in the majority of cases the cures which are recorded are largely due to x-ray and radium therapy. The lesion is not particularly radiosensitive and requires large amounts of irradiation to control it. Three of 6 five-year survivals are attributed to the use of x-ray and radium without curettement. An amputation alone proved successful in 1 case. It, therefore, seems logical to recommend radium

or x-ray therapy (Coutard method) following exploration, unless the tumor occurs in a bone which can be resected without sacrifice of function.

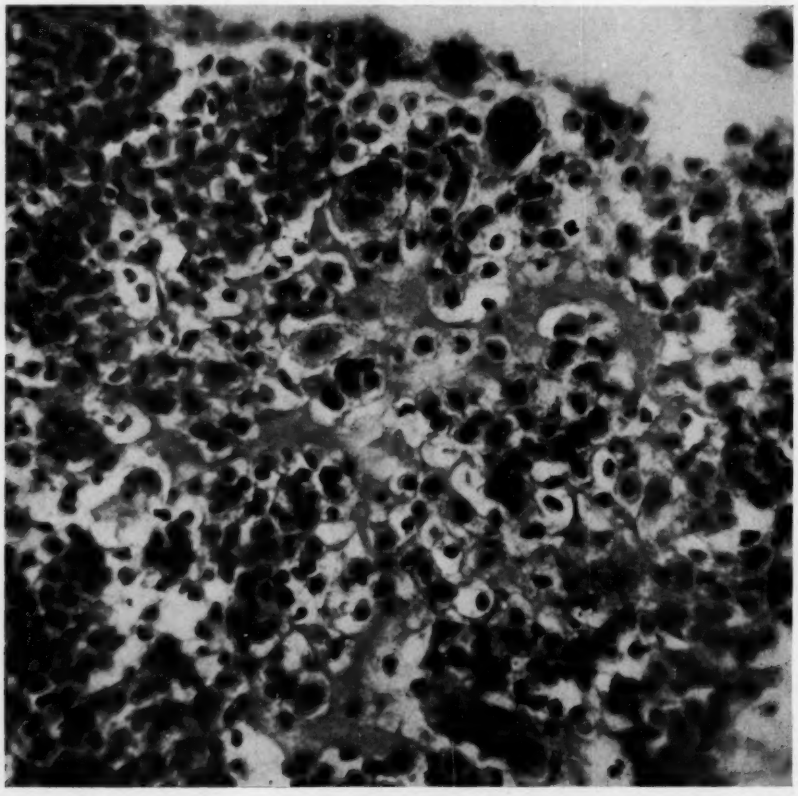

Fig. 4.—Photomicrograph of chondroblastic sarcoma. Note the proliferation of chondroblasts with small amounts of calcified cartilage. Giant-cell invasion about the area of calcification is taking place. While not radiosensitive, the majority of five-year survivals in this tumor have been effected by intensive irradiation.

Osteolytic Osteogenic Sarcoma.—This is a destructive tumor arising in the region of the marrow cavity in the shaft of the long bones.[1, 2] It seems to be related to the formation of cancellous bone which normally follows in the wake of calcified cartilage.

Clinically, the tumor is usually observed about one year after the beginning of symptoms. It has a wide age distribution, being most frequent in young adults. The tumor has an unusual tendency to involve the shaft and to produce a pathologic fracture.

The roentgenograms may be hard to interpret and are often confused with benign bone cyst, giant-cell tumor, metastatic carcinoma, and Ewing's sarcoma.

The distinguishing features in the x-ray film are the melting away and perforation of the bone shell at an early stage when the lesion is asymmetrically located, the presence of a periosteal reaction, and the slight degree of cortical expansion. In advanced cases osseous destruction leaves little doubt of malignant change in the bone.

Microscopically, large spindle cells and large abortive osteoblasts with numerous mitotic figures and small amounts of osteoid tissue are seen (Fig. 5).

Radiosensitivity: The tumor is not sensitive to x-ray or radium and does not respond to therapeutic doses.

Amputation only has been effective in giving 7 (10 per cent) five-year survivals.

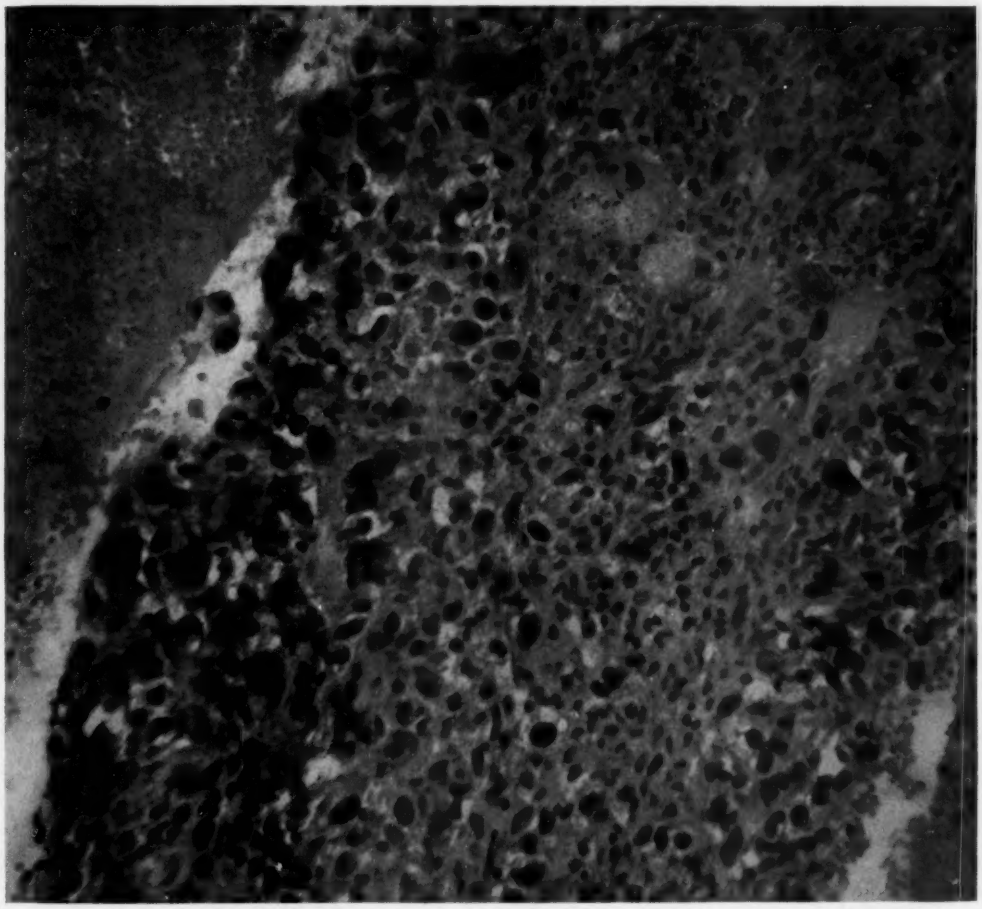

Fig. 5.—Photomicrograph showing abortive osteoblasts, hyperchromatism, and pleomorphism typical of osteolytic osteogenic sarcoma. Large vascular areas are frequently found in this tumor. It is quite radioresistant.

III. CERTAIN TUMORS OF NONOSSEOUS ORIGIN INTIMATELY CONNECTED WITH THE BONE

1. *Ewing's Sarcoma.*—This malignant tumor which arises intracortically or subperiosteally occurs in the first two decades of life; it involves the metaphysis primarily, most often affecting the long pipe bones, especially the tibia and femur.[1, 2, 34] The disease never involves the epiphysis primarily. It shows the usual symptoms of pain and tumor followed by dysfunction.

In the roentgenogram a widening of the shaft, with increase in cortical structure and onion-peel periosteal reaction, is an early finding followed later by varying degrees of bone destruction.

Microscopically, the tumor is composed of small round cells, with dense nuclei and scanty cytoplasm simulating a lymphosarcoma (Fig. 6).

Irradiation provides a good therapeutic test and the best available palliative therapy. Irradiation alone, however, is not sufficient to control the disease in the majority of cases.

A review of our patients,[1, 34] the Bone Sarcoma Registry[35] cases, and the cases of Coley[36] leads to the conclusion that combined preoperative irradiation (Coutard method) in full therapeutic dosage, followed by amputation or radical resection, gives the best results (9 per cent five-year survivals).

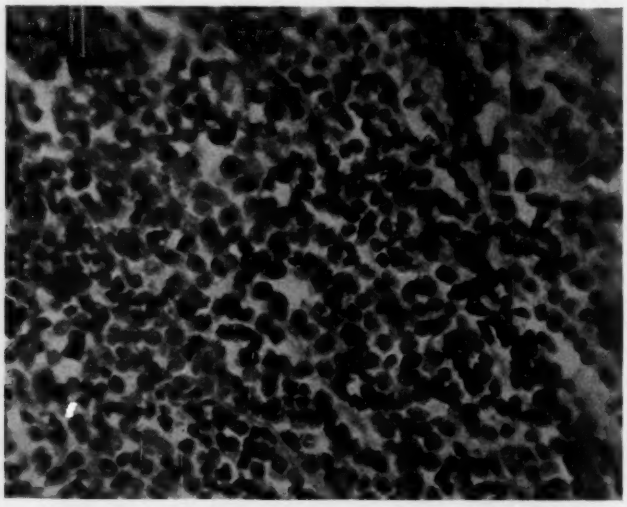

Fig. 6.—Photomicrograph showing the characteristic cells of Ewing's sarcoma. Note the indistinct cytoplasm and the round and oval nuclei. This tumor is quite radiosensitive.

Irradiation alone has been responsible for five-year survivals in 2 of our cases: one a patient in whom the tibia was explored, curetted, and then given intensive x-ray treatment. Another patient clinically showed Ewing's sarcoma in the femur, refused operation, received intensive x-ray treatment. This leg was amputated six years later because of the radiation fibrosis. No residual tumor was found. Resection of the clavicle and a portion of the scapula in successive cases, followed by intensive x-ray therapy, has yielded five-year survivals.

2. *Multiple Myeloma.*—This is a rare form of tumor developing in multiple foci in the red bone marrow of adults.[1, 37, 38] The ribs, spine, pelvis, femur and skull are most frequently affected. The patients are usually in the sixth decade of life. Pathologic fracture occurs in 62 per cent of the cases. Bence-Jones bodies appear in the urine in about 65 per cent of the cases. Remissions of the disease are spontaneous.

In the x-ray picture the lesions show as multiple punched-out areas varying from 1 to 5 cm. or more in diameter. In the skull the area of rarefaction appears between the inner and outer tables of bone.

Microscopically, the tumor is composed of plasmalike cells, with eccentric nuclei containing spokelike arrangement of the chromatin. Fusiform cells and binucleate giant cells are also present (Fig. 7).

The lesion is moderately radiosensitive and among the palliative measures x-ray or radium therapy is outstanding. Control of pain, recalcification of pathologic fracture and areas of bone erosion have been accomplished under this treatment. Symptomatic improvement is the rule and life may be prolonged from two to four years.

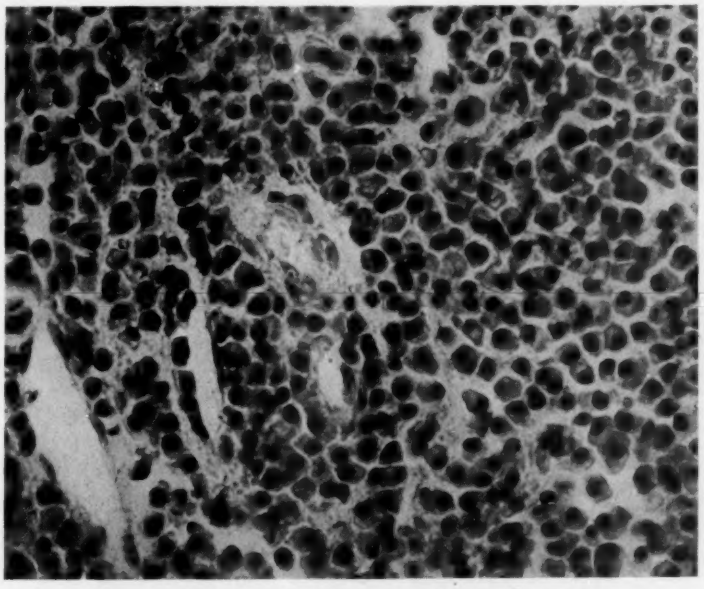

Fig. 7.—Typical plasma cell type of multiple myeloma. This tumor is moderately radiosensitive.

3. *Fibrosarcoma* may be of periosteal (fascial sheath) or neurogenic origin.[1, 3, 30] It may extend in two directions both outside and beneath the periosteum. This form of sarcoma represents only about 1.5 per cent of all neoplasms of bones. The majority of periosteal fibrosarcomas are of a low degree of malignancy. The age of the patient is usually well over 30 years. In only 2 cases of neurogenic sarcoma studied by us was the lesion found in a child. The average duration of symptoms is about one year. It most frequently involves the femur and tibia, but other bones may be affected.

In the x-ray picture there is usually a large soft-part shadow. The bone shows erosion from without. The reaction of the bone is variable. The periosteum may show varying degrees of distorted ossification or no response at all. Bone destruction may be extensive. The ratio of soft-part tumor to bone destruction is important.

Microscopically, the spindle cell varies from the more aggressive oat-cell type to the large fusiform spindle cell, with transition cell forms (Fig. 8). There is usually no bone or cartilage seen in the fibrosarcomas. A definite percentage of the fascial sheath tumors are not sarcomas but cellular fibromas. This accounts in part for the unusual number of cures of so-called fibrosarcoma.

These tumors are not highly radiosensitive. The cell differentiation is all important in this group. There is some evidence that irradiation inhibits tumor growth for a time, producing a slow sclerosing reaction in the fibrospindle-cell type of lesion. Cases with the fibrospindle-cell variety of tumor will survive five years or longer, no matter the inadequacy of the treatment. Amputation or radical resection cures the majority of patients.

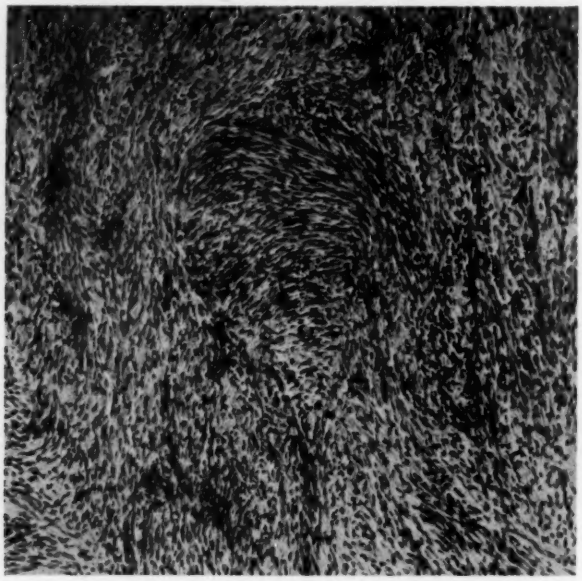

Fig. 8.—Low-power photomicrograph of the fibrospindle-cell sarcoma. The prognosis in this grade of fibrospindle-cell sarcoma following a radical operation is extremely favorable. This tumor is radioresistant.

The undifferentiated oat-cell type of fibrosarcoma is extremely aggressive and neither x-ray treatment, radium, nor local excision offers a permanent cure. Primary amputation where possible is the treatment of choice.

The neurogenic sarcomas, invading bone, are differentiated microscopically by the myxomatous structure intermingled with the fibrous tissue. Nuclei are longer and deeper staining. Many tumor giant cells are seen.

Clinically, and in the roentgenogram these neurogenic tumors bear a close resemblance to the lesions of the fibrospindle-cell series just discussed, though more pronounced destruction of bone is noted. As in the fibrospindle-cell tumors, there is a gradual transition among the

neural tumors from the benign neurofibromas to the most malignant form of neurogenic sarcoma. The more malignant and cellular forms predominate the picture where bones are involved.

Neurogenic sarcomas as a group are highly radioresistant tumors. Interstitial irradiation by buried radon implants has been almost uniformly disappointing. A certain number of cases has shown some regression by external irradiation alone.

It may be stated, however, that clinical cures in neurogenic sarcoma, are obtained only by surgical intervention. The best results are obtained by early amputation, and even with this radical form of treatment, permanent cures are not numerous.

4. *Metastatic carcinoma* of bone is usually seen in late adult life.[1, 2, 39-41] It affects the bones in an extremely variable manner. About one-half of the lesions may occur as a single focus in the ends of the long bones, producing a central area of bone destruction, while the other half may involve the skeleton diffusely, producing either osteolytic or osteoplastic changes. The source of the tumor varies, but the most frequent sites of the primary growth are: cancer of the breast, hypernephroma, cancer of the prostate, thyroid, and somewhere in the female genitals or gastrointestinal tract. Solitary areas of metastatic carcinoma to bone occur most frequently in the spine and in the upper end of the humerus or femur, and are extremely rare below the knee or elbow. They may also involve the trunk or the skull. A central area of bone destruction as seen in the x-ray, rapidly increases and destroys the cortex from within, outwardly with little bone expansion. Multiple areas of skeletal involvement by metastatic tumors may also be osteolytic in character and central in location. Such lesions have a tendency to involve the pelvis and the spine in addition to the upper ends of the humerus and femur. Pathologic fracture is common. In the roentgenogram they are visible as confluent and mottled areas of bone destruction in medullary locations. Osteoplastic involvement of the bones by skeletal metastases is most frequently a diffuse affair, and in addition to the absorption of bone always present, there is a laying down of irregular new bone of moderate density.

The outcome of these cases is uniformly fatal, but palliation and prolongation of life may be achieved by irradiation with x-rays or radium, and some of these patients may live for a period as long as five years.

No rule can be laid down as to treatment. The general condition of the patient must be considered, and a careful balance must be maintained between the amount of irradiation given and the benefit rendered.

5. *Angioma of bone* is considered rare.[1, 42, 43] We have observed only 12 cases. The ages of the patients vary between 4 and 40 years. The tumors are located in the humerus (4 cases), ulna, radius, femur, os calcis, skull, and vertebrae.

The roentgenographic picture is one closely resembling giant-cell tumor or polycystic disease of the bone. In addition, however, one may see isolated cysts beyond the main point of destruction. The trabeculae traversing the cystic cavities vary in density, more so than in giant-cell tumor.

These lesions at exploration show cystic destruction with or without vascular tissue lining the walls. The cysts contain fluid as a rule. The vascular tissue obtained is characteristic of angiomatous tissue elsewhere.

On reviewing the literature, one gains the impression that the majority of the angiomas of bone are of the cavernous type. In our cases, many showed the capillary type of angioma and 2 with proliferative changes suggested malignant change.

Angiomas affecting bone are essentially benign. They show varying degrees of radiosensitivity and the younger the patient the more effective the irradiation. This factor is also present in angiomas found in other parts of the body.

Isolated examples may be pointed out as having been cured by x-ray therapy alone or by surgical intervention.

6. *Recurrent myositis ossificans* may be divided into the traumatic and atraumatic forms arising about the thigh, arm, elbow, neck, and lumbar muscles.[1, 44]

Occupation played little or no role in the case histories studied. Injury was definitely an important factor in 60 per cent of the lesions.

The age incidence varied between 10 and 72 years.

The earliest physical sign after injury is the development of a soft, compressible mass which soon becomes indurated.

Bone may be detected in the roentgenogram within three weeks after the onset of the tumor formation. Small dense areas of calcification soon assume large proportions forming a large spicule of bone, usually separated from the shaft of the neighboring bone. Many lesions gain their maximum growth in six weeks or more and then spontaneously regress or become quiescent.

Histologically, degeneration of muscle, hyperplasia of connective tissue, and organization of hemorrhage are early findings, while osteoid tissue with marrow spaces, osteoblasts about spicules of bone, occasional islands of cartilage (30 per cent of cases), and benign myxomatous tissue represent fully developed myositis ossificans. Malignant changes may complicate myositis ossificans, but this is exceedingly rare.

Myositis ossificans progressiva,[45] a special form of the malady, usually begins in childhood; it affects the spinal muscles primarily. As the name implies, it eventually involves the muscles of the entire skeletal system.

A conservative form of treatment is desirable in the majority of cases. Postoperative recurrences are frequent if surgical removal is employed too early (under 6 months), or if excision is inadequate.

There are isolated cases which have had successful regression of bone recurrence following therapeutic dosages of x-rays. Insufficient experience with this agent on myositis ossificans prevents any final evaluation of the results obtained.

7. *Hand-Schüller-Christian's Disease.*—This group of bone lesions is presented as an example of the so-called xanthomatoses involving congenital disturbances in lipoid metabolism.[1, 46, 48] Organs connected with the reticuloendothelial system reveal a variety of changes. The disease usually makes its appearance early in life and is rarely seen after childhood. The clinical manifestations are variable. Exophthalmus, diabetes insipidus, pigmentation of the skin, and splenomegaly may be seen.

Bone changes are a constant finding and roentgenographically appear as large, rarefied defects, clearly demarcated in the skull and in other flat bones. Diffuse cystic areas may also be seen in the long bones with thinning of the cortex. There is no periosteal reaction.

The blood picture may show a severe anemia.

Histologically, large macrocytes, often binucleated, are the characteristic cells, together with eosinophiles, plasma cells, and lymphocytes. The lesions are quite radiosensitive and the affected bones often reossify under x-ray therapy. Great care must be exercised in giving the treatment to prevent overwhelming anemia. Transfusions are frequently indicated during the period of active roentgen therapy. Small divided doses are best tolerated.

COMMENT

The radiosensitivity of a tumor depends upon both the histologic characteristics of the tumor cells and the nature of the surrounding tumor bed.[49] It cannot be determined by microscopic examination alone. There are innumerable factors to be considered, some of which are not clearly understood at the present time.[50, 51, 53]

Practical knowledge of radiosensitivity has been gained by trial and error, correlating the effect of treatment upon the tumor cells, the variations in the surrounding medium of the tumor, and the ultimate results.

As treatment methods change, ideas of radiosensitivity are revised. Ideas of today may be obsolete tomorrow.

Radiosensitivity increases with the embryonal quality of the tumor or anaplastic changes in the tumor. This statement must be qualified immediately for those tumors which seem to have inherent radioresistant growth properties.[30]

The tumor bed is of great importance, and where cartilage and bone are concerned, two factors make for radioresistance: (1) very little

reaction to irradiation by the individual cells; (2) an avascular type of tumor bed. Edema and infection also increase resistance.

It is certainly true that radiosensitivity does not parallel radiocurability. A cellular neoplasm such as Ewing's tumor is extremely sensitive to irradiation, yet the curability of the disease is far less striking. Of course, it may be argued that large doses of x-ray causing an initial favorable response but failing to sterilize the tumor show the resistant viability of the new growth. This introduces a different interpretation of the term radiosensitivity.

Tissue differentiation, resulting in growth restraint is a most important factor in altering the prognosis, despite the tumor's possible inherent radioresistance or sensitivity (Fig. 9).

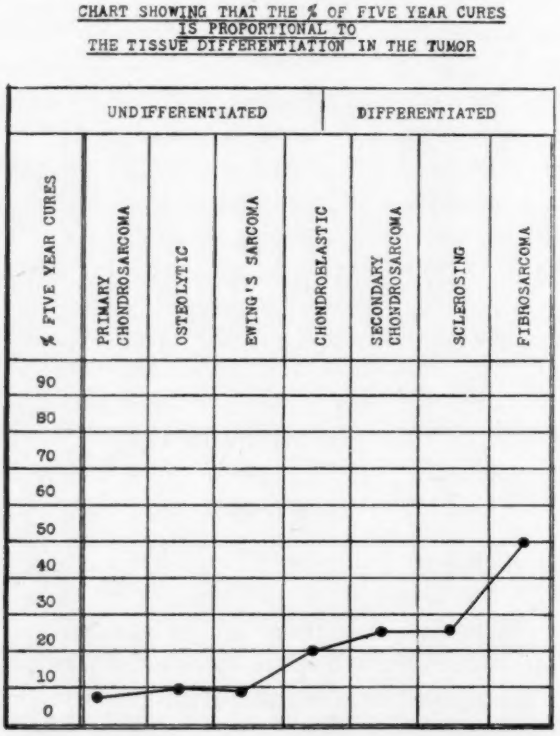

Fig. 9.—To illustrate the influence of tissue differentiation upon five-year survivals despite the radioresistance or multiple types of therapy used.

It is this underlying factor which permits repeated insults to certain tumors, and in spite of them, the patient survives in a number of instances.

Ferguson[52] in a recent publication decries early amputation and points out the number of cases of "osteogenic sarcoma" surviving, which frequently had late amputation often with preliminary x-ray treatment, repeated excisions, or partial resections before amputation was performed. He suggests the possibility that these procedures may have had a favorable influence upon the course of the tumor. I cannot accept this point of view.

If one separates osteogenic sarcoma into the various entities, detailed elsewhere in this paper, and considers the prognosis and treatment of each, and if one further considers the tissue differentiation of each, with its relative aggressiveness, it would seem that the following points are fundamental:

1. Regardless of the type of sarcoma, irradiation alone has rarely sufficed to accomplish a cure, while combined with resection it has offered better results.
2. Amputation is favored as a method of treatment.
3. Tumors with long preoperative symptoms are less aggressive in character and the patients survive in larger numbers.
4. Tumors with short preoperative symptoms usually connote a more aggressive process, with a reduction in case survivals.
5. The primary bone sarcomas which show the greatest tissue differentiation yield the largest percentage of cures when treated adequately.
6. Early diagnosis and aggressive treatment is to be recommended.

Chondroma and *osteochondroma* are radioresistant.

The *various forms of osteogenic sarcoma* are in general radioresistant. Nothing more than transient improvement in proved cases has been noted in the irradiation of these cases. We have observed an occasional sarcoma sterilized by x-ray treatment but the function of the extremity was also destroyed and, needless to say, surgery would have been more comfortable and adequate in the beginning.

Radiation is of advantage in those patients where palliation is desired or in technically inoperable locations.

Chondroblastic sarcoma is controlled by irradiation despite its inherent radioresistant qualities.

Many *giant-cell tumors* of bone are radiosensitive, though the tissue changes which occur are hard to explain. Overtreatment must be guarded against, as devitalized normal bone does not make for a satisfactory result.

Certain facts can be stated which seem to be closely related to failure in treating giant-cell tumor by irradiation or by surgery: (1) too early weight-bearing of the affected part; (2) perforation of the bone shell by the tumor before treatment is instituted; (3) inadequate therapy; (4) the declining healing power of bone due to age.

Multiple myeloma is moderately radiosensitive. The larger the area of bone destruction, the less satisfactory is the response. Palliation by moderate doses of irradiation is satisfactory, however, and partial sterilization of the tumor process may be obtained for awhile.

Fibrosarcoma is not usually radiosensitive and only very low grade malignant tumors may be controlled by escharotic doses of therapy.

Bone involvement by *metastatic carcinoma* may show marked palliative response to x-rays or radium.

Angioma of bone cannot be generalized upon, but isolated cases have been completely controlled by roentgen therapy.

Data on *recurrent myositis ossificans* are insufficient to recommend irradiation as a routine procedure.

Hand-Schüller-Christian's disease is quite sensitive to the x-rays and favorable results are the rule if the patient is kept under periodic and careful observation.

Many diseases not primary in bone but affecting it have not been mentioned. A sufficient variety has been presented, however, to illustrate the trend of treatment in the various groups.

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ASPIRATION BIOPSY

Further Observations With an Improved Instrument

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AT THE outset, we visualized an appliance for the performance of aspiration biopsy that would furnish a section of tissue for study showing the various structures in continuity. This was in contrast to the methods then in use, their technique being based upon smear preparations of particles of tissue and the diagnosis made from cytologic appearance alone. We were willing to concede that in the hands of experts with long training in this type of observation satisfactory evaluations could be accomplished. This was of necessity not true in the case of the worker occasionally called upon to perform an examination by this method.

It was thought that an instrument patterned after a druggist's cork borer with the cutting edge serrated might prove of value if fitted with an exceptionally sharp trocar. After a suitable plug of tissue had been encircled, it was planned to imprison it within the lumen of the cannula and sever its attachment by twisting the syringe in such a manner that its base would be brought into contact with the sharp roughened edges of the instrument.

Proceeding with this idea in mind, a large bore spinal puncture needle was cut down, its cutting edge ground very sharp and in a serrated manner. Its stylet was likewise made exceptionally keen. For aspiration purposes a 10 c.c. record syringe was employed. We soon learned that it was essential to be in a position to lock the plunger of the syringe at the maximum excursion of its upstroke. After searching the market and finding such an appliance not to be available, one was extemporized by filing a notch on the shank of the plunger and having a spring catch placed upon the housing of the syringe barrel. With this rather crude extemporized outfit we were enabled to do fairly satisfactory work. About two years ago our original paper covering its application was published;[1] since that time with the aid of the research staff of Becton, Dickinson Co., Rutherford, N. J., a much more technically satisfactory instrument has been made generally available.

The principle behind our original idea has been adhered to, but the new device has many convenient improvements; among them is a thumb rest at the head of the stylet and a convenient finger rest beneath. An unusually sharp flat cutting edge has been placed upon the trocar. Thanks to the ingenuity of Dr. Oscar Schwidetzky, of Becton, Dickinson Co., a simple catch patterned after those used to hold umbrellas open

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Fig. 1.—*1*. A typical case suitable for aspiration biopsy. The patient is a young woman and the lesion under investigation is a submaxillary tumor. Obviously, a cutting diagnostic operation would prove to be undesirable. *2*. After the skin has been properly prepared and anesthetized, the meshed trocar and cannula are thrust through the wheal formed by the injection of the anesthetic and into the periphery of the tumor. The trocar is then removed and the syringe attached. *3*. The instrument is driven several millimeters further into the tissue and vacuum is created by drawing syringe to maximum excursion where it is automatically locked. This vacuum is held for three minutes. The tissue plug is severed by a twisting motion, accomplished by turning syringe, bringing base of plug into cutting edges of cannula.

has been applied to the shaft of the plunger. It is very positive in action and simple to operate.

Our technique has remained unchanged from the original report but is summarized here:

1. A suitable antiseptic is applied to the skin area over the site of proposed puncture and a wheal is formed by novocain or other local anesthetic of choice.

2. The meshed trocar and cannula are thrust through the site of anesthesia and into the periphery of the tumor under investigation. (Some prefer to make a small nick with a knife before introducing the instrument. We feel that this is advantageous in certain areas, especially about the neck where sudden penetration of the needle under force might prove disastrous.)

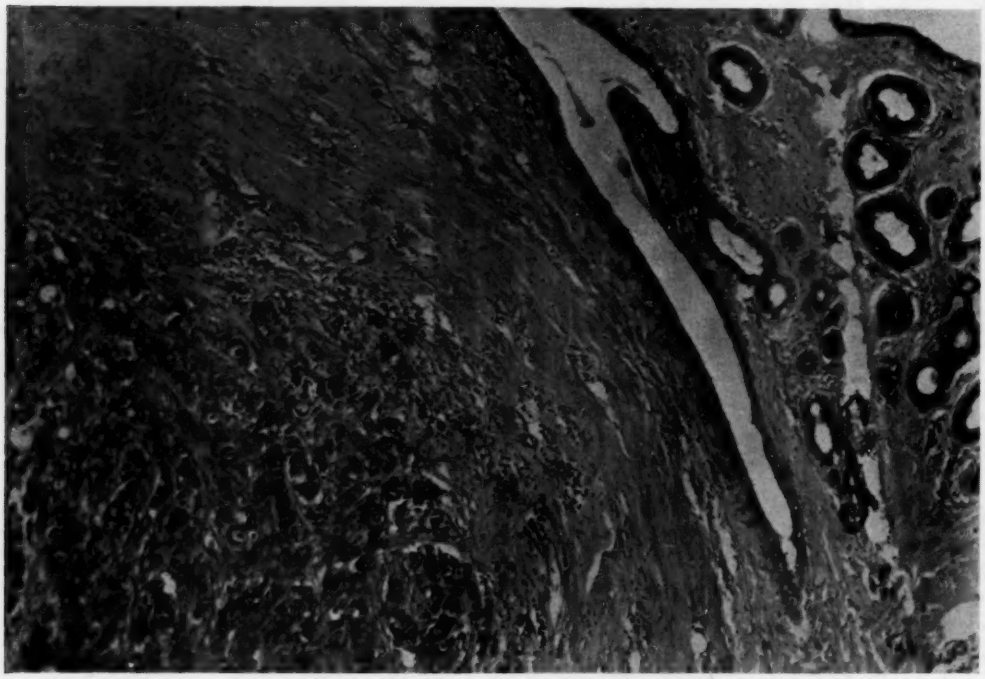

Fig. 2.—Illustrating a commonly encountered potential pitfall in aspiration biopsy diagnosis. The specimen is a section cut from a breast tumor showing benign fibroadenoma in upper and right (*R*) aspect. In the lower left (*L*) it is definitely cancerous. Quite obviously, there is a possibility that material could be aspirated from the nonmalignant regions that would give an entirely false and dangerous impression. For this reason, we have had forced upon us the decision to disregard negative evidence obtained in this manner, and when it is encountered, to make further investigations. (Courtesy of Army Medical Museum, Washington, D. C., and Lieut. Col. J. E. Ash, Medical Corps, U. S. Army.)

3. The stylet is removed, the syringe attached, and the cutting edge of the cannula is pushed by using a gentle rotary movement several millimeters further into the site from which the biopsy is sought.

4. The vacuum is now drawn, the piston locked at its maximum excursion, and the cannula slightly advanced. We have found it advantageous to hold this vacuum for *three minutes* before attempting to free the tissue plug.

5. At the expiration of three minutes, an arc is described with the syringe at a 45 degree angle in an endeavor to bring the plug of tissue into contact with the cutting edges of the cannula, thus severing it.

6. The instrument is withdrawn and the contents are expressed into normal saline solution. This solution should be used to flush the syringe and needle as at times the specimens may be recovered by this means when others fail. The advantage of this procedure is that specimens sufficiently large to fix, cut, stain, and mount in the usual manner are obtained. In another publication, we described in detail a technique for handling these small particles.[3] Martin and Ellis have aptly stated[2] that without a sympathetic attitude on the part of the pathologist no progress can be made in this rather difficult field of diagnosis. None of us wish to deny the fact that handling of these tissue fragments is difficult and time consuming.

SUMMARY

1. An improved instrument for taking aspiration biopsies is reported. No material change has been made in the technical procedure originally reported.

2. Aspiration biopsy is always a procedure of necessity, never of election. A number of years' experience has taught us that negative evidence is valueless and is disregarded in our final consideration of the case in question. Positive findings, on the other hand, are taken at face value.

3. We have found the application of this method especially valuable in lesions about the face and neck, especially in women by whom a cutting operation for diagnostic purposes would not be tolerated. Its value has been proved in the case of bone tumors also.

4. Aspiration biopsy is "the hard way." There is nothing easy about it, from the standpoint of either taking the specimen or tediously preparing the microscopic sections.

5. Extreme care must be used in the vicinity of great vessels and other vital structures as the instrument used is capable of inflicting serious damage.

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THE USE OF A COLD AIR BLAST ON PRECANCEROUS SKIN LESIONS AND HEMANGIOMAS

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DRY carbon-dioxide ice in the solid form has been used very successfully for the treatment of small capillary hemangiomas in babies. Excision and sclerosing solutions have been used for the larger capillary and cavernous types of hemangiomas. A need has been felt for a modification of the freezing technique to be used on the medium-sized hemangiomas and those resistant to a single carbon-dioxide ice treatment. This direct application of carbon-dioxide ice to the skin, for more than ten seconds, over a small area causes a chemical burn with destruction of the skin and a permanent scarring. The use of radium may be objected to on the basis of the late carcinogenic action in these essentially benign lesions in babies.

A further need has also been felt for a simple, readily available method for removing precancerous, keratotic lesions from the skin, which will not cause a permanent scarring of the area. The radon bulb, which has long been used for the purpose, is not always available and is expensive to provide for only a few patients at a time. Electric cauteries and caustics, which are also effective for the lesions, tend to produce considerable scarring.

A method of freezing localized areas of skin and subcutaneous tissue of between 3 to 5 cm. in diameter to a depth of 0.5 to 1 cm., without causing a permanent destruction of the overlying epidermis, was worked out, as described.

EQUIPMENT AND TECHNIQUE

A current of compressed air is blown through a coil of metal tubing packed in carbon-dioxide ice. A nozzle is placed on the end of the tubing by means of which the blast of air is played on the skin lesion to be treated. The compressed air is obtained from one of the hospital outlets to which the coil is attached by a piece of heavy rubber tubing securely fastened at each end. The air pressure in this institution is maintained at about eighty pounds per square inch. A section of $\frac{3}{8}$ inch copper tubing, about 40 feet long, is wound into a convenient coil to fit in a standard-sized pail. About ten pounds of carbon-dioxide ice is then broken up and packed around the coil of pipe. Insulation

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around the pail and over the ice will make it last much longer. A very short length of insulated hose is then used to connect a nozzle to the coil. This should not be more than 10 inches in length because of the rapid warming of the air in passing through it. A short piece of glass tubing drawn to a point can be used as a nozzle. The opening of the nozzle may vary from 2 to 4 mm. in diameter.

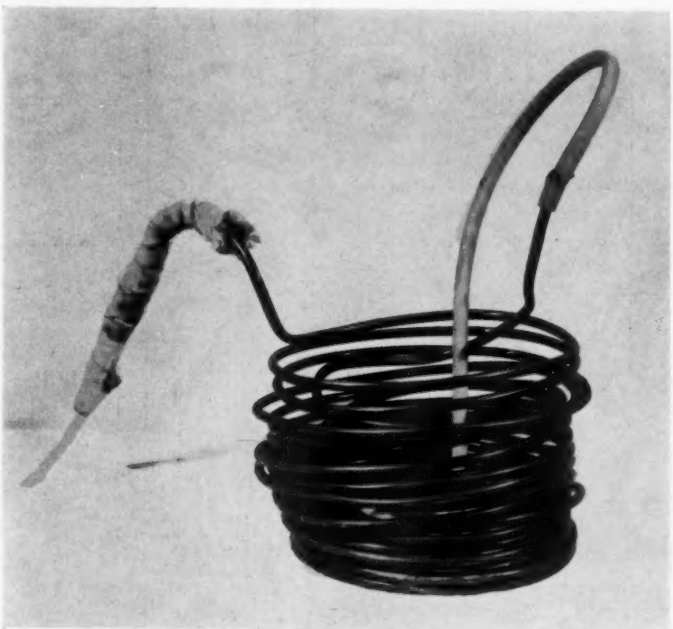

Fig. 1.—Coil of copper tubing with insulated nozzle used to cool the air blast.

If the apparatus is to be used to treat a number of patients successively, so that it will be operating over considerable periods of time, an intermediate drying chamber must be connected in the air hose before it enters the cooler. This is necessary in order to remove the moisture which would otherwise condense and freeze in the cooler, thereby obstructing the air flow, if used more than five to ten minutes at a time. Passing the air through a few centimeters of soda lime in an airtight chamber seems sufficient to dry it out adequately for this purpose.

Only a few seconds are required to cool off the apparatus sufficiently for use after the air has been turned on. A strong blast of cold air, which registers between –15 and –20° C., is directed on the lesion, the nozzle being held 1 to 3 cm. above the skin surface. The area frozen depends upon the size of the nozzle, the distance between the nozzle and the skin, and the time period during which the air is applied. A 0.5 cm. lesion can be treated over a 1 cm. area by holding a 2 mm. nozzle about 1 cm. above the skin surface for twenty seconds.

TABLE I

RESULTS OF AIR BLAST TREATMENTS ON PRECANCEROUS SKIN LESIONS*

NO.	NAME	LESION			TREATMENT		RESULT	
		LOCATION	SIZE	NO.	TIME (IN SECONDS)	NO.	TIME (AFTER TREATMENT)	LESION
1	C. W.	Dorsum (right hand)	3.0 cm.	4	45	2	4 wk.	Disappeared
2	C. O.	Left forearm	3.0 cm.	3	45	2	4 wk.	Disappeared
3	J. M.	Right ear	0.5 cm.	1	20	1	2 wk.	Disappeared
4	H. B.	Nose	0.5 cm.	1	18	1	4 wk.	Disappeared
5	A. E.	Face	0.5 cm.	1	20	1	4 wk.	Disappeared
6	R. H.	Forearms	1.0 cm.	3	20	1	4 wk.	Disappeared
7	C. K.	Face	0.8 cm.	5	20	1	4 wk.	Disappeared
8	T. O.	Face	1.0 cm.	1	25	1	4 wk.	Disappeared
9	J. O.	Cheek	2.0 cm.	1	37	1	4 wk.	Disappeared
10	M. P.	Face	0.8 cm.	2	25	1	4 wk.	Disappeared
11	H. R.	Forehead	0.5 cm.	1	20	1	4 wk.	Disappeared
12	J. S.	Ear	0.5 cm.	1	20	1	8 wk.	Unchanged
13	M. T.	Hand, shoulder, and chest	2.0 cm.	1	30	1	6 wk.	Disappeared
14	E. R.	Forehead	0.8 cm.	1	25	1	2 wk.	Disappeared

*Lesions treated, 28; lesions cured, 27.

TABLE II

RESULTS OF AIR BLAST, SUPPLEMENTED WITH DRY ICE TREATMENTS, ON HEMANGIOMAS IN CHILDREN

NO.	NAME	LESION				TREATMENT			RESULT	
		NO.	TYPE	SIZE	LOCATION	TYPE	TIME	NO.	TIME	LESION
1	F. B.	1	Capillary	2 by 2.5 cm.	Right buttock	Air	20 sec.	1	3 wk.	Blanched
						Ice	10 sec.	2	8 wk.	Disappeared
2	L. C.	1	Port wine	3 by 4 cm.	Right cheek	Air	25 sec.	6	16 wk.	Blanched
3	E. R.	1	Capillary	1.5 by 3 cm.	Antecubital	Air	25 sec.	3	6 wk.	Disappeared
4	W. B.	1	Port wine	3 by 5 cm.	Right cheek	Air	30 sec.	3	10 wk.	Improved
5	J. K.	1	Capillary	2 by 3 cm.	Right leg	Air	60 sec.	1	6 wk.	Cured
6	B. W.	1	Capillary	1.5 by 2 cm.	Left leg	Air	20 sec.	2	6 wk.	Cured
7	M. F.	3	Capillary	1.5 by 2.5 cm.	Abdomen	Air	20 sec.	3	10 wk.	Cured
				1.5 by 2 cm.	Right arm	Air	20 sec.	3	10 wk.	Cured
				1 by 0.5 cm.	Back	Air	20 sec.	3	10 wk.	Cured

RESULTS

A pitted, frozen plaque is immediately formed. This disappears in a few minutes, leaving an erythematous area which may become crusted over in two or three days if the treatment has been more than twenty seconds. This crust usually falls off within ten or twelve days, permitting a second treatment to be given within two weeks, if indicated.

Fig. 2.—Keratotic lesions on dorsum of right hand and forearm of Patient 1 before treatment. This patient developed a large squamous-cell carcinoma on the dorsum of the left hand from a similar lesion.

Experimental use of this method on rabbits' ears and abdomens showed that a maximum treatment of any single area should not be more than sixty seconds to avoid destruction of the skin and damage to the deep tissues. Treatment of from three to five minutes caused an ulceration which extended through the entire thickness of a rabbit's ear or caused peritonitis, if used on the abdomen.

COMMENTS

The results obtained by this method of indirect freezing of precancerous skin lesions have been very successful, with complete disappearance of the treated lesions in all but one case (Case 12).

This particular lesion originated from freezing the ear a number of years previously which may account for its intractability to further freezing treatment. The only cases listed here are those in which an adequate follow-up has been obtained, although a much larger number of precancerous lesions have been treated. Several of these patients have had one or more skin cancers which have already developed from similar keratotic lesions. Precancerous lesions near the eye should not be treated by air because of the ecchymosis produced in this region.

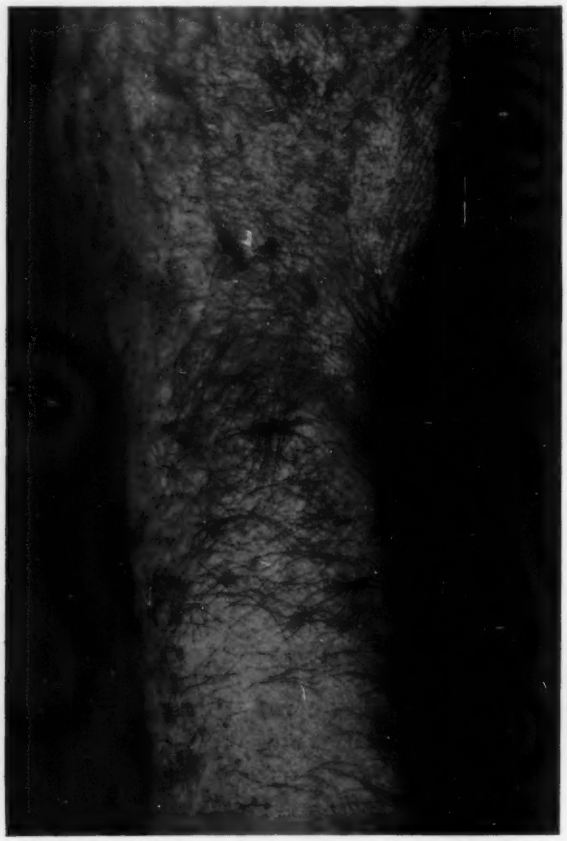

Fig. 3.—The right hand and forearm of the same patient four months after treatment with the cold air blast.

The use of this method has been restricted to the larger hemangiomas, and the results on these lesions have been superior to those previously obtained with repeated application of solid carbon-dioxide ice. The superior results obtained by this method are due to the larger area which can be covered during a single treatment with less ulceration, crusting, and subsequent scarring. Several mothers who have seen the results of both types of treatment have requested the air blast in preference to the dry ice in view of its minimal reaction on the skin. It is occasionally necessary to touch up small pseudopodia around the edges

of a large lesion with small amounts of carbon-dioxide ice, after the main body of the hemangioma has disappeared following a single air blast treatment.

Several attempts have been made to treat port-wine marks by this method with only moderate success. A certain amount of blanching occurs over the treated area without any scarring, which is a definite improvement over direct treatment with dry ice. No complete disappearance of a port-wine mark has, as yet, been noted.

CONCLUSION

1. The indirect freezing of large hemangiomas and precancerous skin lesions by an air blast is a relatively simple and economical method of removing these lesions.

2. A definite advantage over the more caustic agents is present in that the residual skin defect is minimal compared with that resulting from the other methods mentioned.

TREATMENT OF MAJOR WOUNDS OF THE SKULL

I. Cerebral Fungus: Treatment by Skin Grafting

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IF A major cranial defect is sustained so that an area of cerebrum one inch or more in diameter is exposed and becomes infected, a herniating mass of infected and inflamed brain tissue will usually ensue. The infected hernia cerebri is commonly referred to as a fungus. I feel certain that the lesion is not nearly so common now in civil life as it was twenty years ago in spite of the increasing incidence of head injuries. This fact in itself is evidence for the increasingly better management of acute head injuries. Nevertheless an occasional fungus appears to be unavoidable, and in war surgery the lesion is a relatively prominent one. After having developed, it presents itself as a real problem. The fungus is highly intractable to treatment and often it ultimately leads to fatality. The surgeon is sooner or later tempted to amputate the herniating mass flush with the skull, only, as in the case of the Lernaean hydra, to be confronted by a recurrence, if, indeed, death is not precipitated by meningitis, ventriculitis, or an overwhelming encephalitis.

The histologic evidence of inflammation extends to varying depths from the fungus into the brain. This localized encephalitis with the associated edema and swelling progress in a vicious cycle. This lesion in which there is an absence of skin with exposure of underlying tissues is unique when brain is the underlying tissue. The most important factor which makes the lesion unique is the poor grade of granulation tissue over which epithelium might grow. The only source of granulation tissue from the brain is the fibroblast of the walls of vessels and these are relatively sparse. This fact combined with the slow but progressive herniation of the fungus makes it understandable why epithelium does not grow in from the skin margin as it does in the case of open wounds elsewhere.

It has hitherto been a custom and almost a dictum in neurological surgery that exposed brain should not be covered with gauze but by some smooth tissue such as gutta percha and this type of dressing was used in World War I.[1] Such a dressing does not encourage the development of granulations. Although the source of granulation tissue is deficient, nevertheless a good bed of granulations can be provoked by a dressing of dry gauze as is done in the case of other wounds. Such a bed of granulations has proved to be adequately receptive for small deep skin grafts in two consecutive cases followed by rapid and complete healing

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CASE REPORTS

CASE 1.—Wm. K., an 8-year-old white boy, was admitted to the University Hospital on Dec. 26, 1938. One month previously he had sustained a compound skull fracture in the right frontal region. The wound was débrided but became infected and a fungus developed (Fig. 1).

Fig. 1.—Cerebral fungus in right frontal region before grafting.

The general and neurological examinations were essentially negative except for the local lesion. The intracranial pressure was normal. The fungus had been dressed for some time with plain sterile gauze. When admitted to the hospital the dressings were removed and a fair bed of granulation tissue was noted to have developed on the fungus. The herniation was considerable and by palpation the impression was obtained that the anterior aspect of the right ventricle might be sufficiently superficial to be opened if amputation of the fungus were undertaken. There appeared to be no reason why small skin grafts would not take on the granulations. On Dec. 28, 1938, the entire surface was covered with small deep grafts. Eighty per cent of the grafts took readily. A few in the center of the fungus died. Two more attempts to graft this small area were partially successful and by Feb. 19, 1939, at which time the patient was discharged, epithelization was complete. While epithelization was in progress, the hernia spontaneously receded until it was flat.

The patient returned on March 21, 1939, the wound being completely healed. A photograph was taken at this time (Fig. 2). The wound has remained healed to the time of writing (two years).

Fig. 2.—Photograph of cerebral fungus shown in Fig. 1 taken three months later, showing complete epithelization. The hernia receded spontaneously after it was grafted.

CASE 2.—Wm. McH.,* a white boy, 4 years of age, was admitted to the Children's Hospital of Cincinnati on July 20, 1940. Six weeks before he had fallen from a swing, striking his head. Osteomyelitis and brain abscess developed. The abscess was drained through an opening in the frontal cranium measuring about 1½ by 1 inch. A fungus developed as shown in Fig. 3. The fungus was dressed with gauze, and when the granulations were sufficiently abundant, they were covered by small deep grafts. In eight days the fungus was flat and epithelization complete (Fig. 4).

Before grafting, the patient exhibited an increased intracranial pressure as evidenced by papilledema. A ventriculogram revealed some dilatation of the third and lateral ventricles. Dr. Evans interpreted the situation as one of obstructive hydrocephalus and felt that this was largely responsible for the herniation of the fungus. Concomitant with grafting, therefore, he made a perforation in the third ventricle

*This patient developed a cerebral fungus while on the neurosurgical service of Dr. Joseph Evans, the Children's Hospital, Cincinnati, Ohio. Dr. W. T. McElhinney, having studied Case 1 as a student at the State University of Iowa, suggested that the same methods be applied to Case 2. Prompt healing followed. I am indebted to Drs. Evans and McElhinney for kindly permitting me to include their case in this publication.

Fig. 3.—Cerebral fungus before grafting.

Fig. 4.—Photograph of cerebral fungus shown in Fig. 3 taken eight days following the application of small deep grafts. Epithelization is complete and the herniation has completely receded.

for the purpose of shunting the ventricular fluid into the basilar subarachnoid spaces. It is the opinion of Dr. Evans that this procedure was responsible for the retraction of the fungus as well as the subsequent recession of the increased intracranial pressure and would not attribute the recession to epithelization alone. I am at variance with this view as brought out in the discussion.

DISCUSSION

The two cases reported here illustrate a simple and effective method of treating cerebral fungus. Granulations can be induced on the fungus which will be receptive to skin grafts. A good method of provoking abundant and healthy granulations is the application of plain sterile gauze and this dressing is therefore preferable to gutta percha. Small deep grafts should be used and applied close together covering the entire surface of the fungus. In Case 1 the fungus receded spontaneously as epithelization progressed. It is my opinion that the local encephalitis with its associated edema subsides when epithelization occurs, thus accounting for the retraction of the hernia. The prompt subsidence of infection and its attending signs and symptoms when large areas over the body are grafted is a common observation.

Undoubtedly the end result of a healed fungus involves a firm attachment of scarred brain to skin at the site of the defect. This scar in some cases may later lead to the development of epileptic seizures. However, in such an event and when the infection has subsided, the scar may be repaired in the accepted manner with impunity. The objective in treating the fungus is to save the patient's life.

Upon the completion of this report Dr. Wilder Penfield called my attention to the Proceedings of the Twenty-seventh Meeting of the Society of British Neurological Surgeons.[2]

In a discussion of the treatment of penetrating wounds of the skull, consideration is given by Cairns to the problem of cerebral fungus. The conditions leading to and maintaining a fungus are discussed. In the event that a fungus develops, it is important to establish the presence or absence of complicating factors that might be associated with the fungus, such as abscess or some degree of meningitis. Cairns advocates the use of ventriculography to gain information concerning the possibility of abscess and wisely cautions against needling the fungus unless a ventriculogram reveals the presence of an expanding mass near it. O'Connell points out that the uncomplicated fungus is associated with a quite high protein content in the spinal fluid and a very low or slight pleocytosis.

Wright and Clark-Maxwell report good results from skin grafting the fungus and endorse the method as ideal treatment.

The experience with the cases reported in this paper coincides, therefore, with the experience of the British surgeons. Skin grafting is indicated as treatment of a fungus and not only will greatly hasten its

healing but probably will forestall complications that may attend delayed healing. All efforts leading to skin grafting as a final stage in treatment would seem to be in order.

CONCLUSIONS

1. Granulations may be induced on a fungus cerebri that will be adequately receptive to small deep skin grafts.

2. To this end granulations should be encouraged by dressing the herniated brain with gauze rather than an inert material such as gutta percha.

3. The fungus should not necessarily be amputated. The herniation will recede when epithelization is complete.

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Editorial

Impacted Fracture of the Hip

WHEN is a fracture of the neck of the femur impacted? The term "impacted fracture" of the hip is used frequently by physicians. Unfortunately, the term is too frequently misused. The physician who is responsible for the treatment of the patient and the roentgenologist who assists the physician in the proper interpretation of the x-ray studies of the fractured hip should use the same definition of the term "impacted fracture." If there could be an accepted definition of the term by the profession there would be less confusion, less morbidity, and a greater appreciation of the mechanical principles that are involved in the treatment and in the prognosis of fractures of the neck of the femur.

A true impacted fracture of the neck of the femur always unites by bony union without any special treatment. Nailing operations or any of the other types of operative internal fixation, which are so important in the treatment of fractures of the neck of the femur that are not impacted, are contraindicated. It is, therefore, most important for all of us to accept and teach one and only one definition of the term "impacted fracture."

This fracture presents constant clinical subjective and objective findings and specific radiographic features. Clinically, the fractured extremity can be moved freely and almost painlessly. The patient may even walk after the injury. The severe pain, muscle spasm, external rotation deformity, shortening, and almost complete loss of function of the limb which characterizes the fracture of the hip that is not impacted, are not present. Radiologically, the fracture line through the neck of the femur is subcapital, almost horizontal, and the neck and shaft of the femur are abducted in relation to the head. The normal angle of head, neck, and shaft is increased and a coxa valga deformity is present. The lateral radiogram shows no displacement between the head and neck fragments. These radiographic findings are essential in the diagnosis of "impacted fracture." The fracture is impacted because the mechanical forces between the two fragments are pressure forces and not shearing forces. There is never a true impaction if the normal angle between the two fragments is diminished with a coxa vara deformity because the forces between the fragments are then shearing and not pressure forces. Internal fixation is essential in the treatment of a fractured femoral neck with coxa vara deformity or when the neck and shaft fragment are adducted in relation to the head fragment. All fractures with a coxa valga deformity are not impacted, but all impacted fractures are in a coxa valga position. An abduction fracture

of the neck with a coxa valga deformity is never impacted if the line of fracture is nearly vertical or greater than 30 degrees with the horizontal. Pressure forces between the two fragments must dominate in an impacted fracture. When shearing forces are greater than pressure forces between the two fragments, the fracture cannot be considered impacted.

The true impacted fracture of the hip unites by bony union without any special form of internal or external immobilization. If the fracture is not impacted, operative internal fixation is essential. Impaction is synonymous with mechanical features which favor the domination of pressure forces over shearing forces from transmission of body weight and muscle contraction. An abduction injury with abduction of the distal neck and shaft fragment in relation to the proximal head fragment, coxa valga deformity, an almost horizontal subcapital fracture line as seen in the anteroposterior radiogram, no displacement as seen in the true lateral radiogram, and a fractured limb that can be moved freely and almost painlessly, are the radiographic and clinical features which should be essential in the universal definition of an "impacted fracture" of the hip.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

INTRAVENOUS PENTOTHAL SODIUM ANESTHESIA

A REVIEW OF THE LITERATURE

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THE successful use of pentothal sodium as an intravenous anesthetic by numerous groups, and its recommendation by some as "one of the most valuable advances in the science of anesthesia that has been made in recent times,"[116] makes a thorough consideration of this agent mandatory upon progressive anesthetists and upon surgeons who assume part of the responsibility of directing the anesthetic control of their patients. This review is made in an attempt to evaluate this anesthetic agent. Since it is the opinion of many pharmacologists that there is slight hope of producing additional effective members of the barbiturate group,[3] pentothal sodium may remain the barbiturate most acceptable for anesthesia.

Various intravenous anesthetic agents had been used prior to the introduction of sodium pentothal.[28, 60, 64, 65, 102] The first recorded use of intravenous anesthesia appears to be that of Pirogoff and von Flour, who, in 1847, administered ether in this way, but abandoned the method because of the high mortality. Ore, in 1872 at Lyons, used a solution of chloral hydrate. Remarkable results were obtained by the Russian, Federow, who, during the early years of the twentieth century, reported the intravenous use of 0.75 per cent hedonal for anesthesia in 530 cases without a death. At a later date, Gwathmey[58] used from 5 to 7.5 per cent ether in Ringer's solution intravenously and later reported the use of trichlorisopropl alcohol intravenously. Other drugs which have been suggested as intravenous anesthetic agents at various times include chloroform, morphine sulfate, paraldehyde, and avertin.

The barbituric acid compounds were first introduced as intravenous anesthetic agents in 1929 when an attempt was made to utilize sodium amytal. This drug was abandoned because of the lack of proper relaxation, the postoperative restlessness, and the prolonged recovery period. Although pentothal sodium had been developed earlier, by Tabern and Volwiler,[179] it first was used clinically by Lundy at the Mayo Clinic during the latter six months of 1934.[2, 106, 178] Since that time he and others have reported its use in 54,851 cases with almost universal praise of its anesthetic properties.

PHARMACOLOGIC AND PATHOLOGIC CONSIDERATIONS

Pentothal sodium, or sodium ethyl (1 methylbutyl) thiobarbiturate, owes its success as an anesthetic agent to the fact that like evipal it belongs to the group of so-called "light" or short-acting barbiturates.[28, 80] The "heavy" barbiturates, such as nembutal and sodium amytal, remain unchanged in vivo and are excreted as such by the kidneys for as long as seventy-two hours. For this reason, when they are used as anesthetic agents, there is an undesirable prolongation of the anesthetic effect. Although the method of the destruction of pentothal in the body is not clearly understood, it has been shown that the process occurs so rapidly that scarcely a trace can be found in secretions three to twelve hours after the administration of single therapeutic doses, and for all practical purposes the effect lasts but three to thirty minutes, depending upon the dose which is used.[16, 80, 174] However, after prolonged administration the rate of detoxification is not proportionate to the total dosage, as shown by Kohn-Richards and Grimes,[87] who demonstrated that the rate of detoxification of pentothal given to rabbits by continuous infusion is roughly one-half that after a single dose. Similar results were obtained in an experimental study performed by Kozelka and Hine.[89] Gruhzit and co-workers[56] suggest that normal organs are able to destroy only a limited amount of pentothal or that the organs are so altered by the drug that they lose their capacity for detoxification. Butler and Bush[24, 25] offer experimental evidence that some short-acting barbiturates are transformed in vivo to less active compounds which have a more prolonged but less intense action. Either of these explanations helps clarify clinical and experimental observations of the prolonged and variant effects of large doses of pentothal.

The pharmacologic action of pentothal sodium has been subjected to close scrutiny by numerous investigators.[2, 9, 11, 15, 16, 22-27, 29-31, 39, 52-56, 59, 64, 71, 82, 86, 88-90, 103, 107-109, 116, 123, 128, 129, 131, 135, 146, 147, 153, 155, 156, 159, 161, 162, 164, 172, 177, 179, 182, 186, 92, 197-200] Its effects upon the circulatory system are minimal, no significant changes having been observed clinically in the pulse volume and rate, the blood pressure,[30, 31, 82, 116] or electrocardiographic tracings.[15, 29, 30, 86, 116, 159, 182, 197] The occasional appearance of conduction changes, as indicated by ectopic beats,[55] has been explained on the basis of a transitory anoxemia, the relief of which causes the resumption of normal rhythm. Cardiac irregularities, already present, have not been affected by sodium pentothal anesthesia.[182, 197] The well-recognized vasodilatation which accompanies administration of pentothal has been utilized in diagnostic tests for peripheral vascular disease[199] and as a prognostic agent in the preoperative consideration of essential hypertension.[11]

Investigations by Reynolds and Veal[153, 155, 156, 192] suggest the possibility that continuous administration of small amounts of pentothal

sodium may result in heart muscle poisoning. To a series of dogs they gave repeated minimal narcotic doses, finding that there was a progressively longer narcotic effect after each injection. In every instance, death followed a sudden drop in blood pressure to zero, a termination which occurred without warning and in the absence of respiratory paralysis. The suddenness of the blood pressure fall and the previous appearance of ectopic ventricular contractions suggested to the authors the development of ventricular fibrillation. The several reports of this group of experiments make no mention of any control of fluid balance or of oxygenation, and for this reason judgment must be withheld as to the validity of the conclusions drawn by the authors. It is Mousel's opinion[128] that cardiovascular collapse is secondary to anoxemia caused by prolonged respiratory arrest. No such occurrence of cardiac failure during pentothal anesthesia is recorded in the clinical reports.

Pentothal sodium causes a very definite respiratory depression which is clearly demonstrated by a shallowness of breathing without change in the respiratory rate. Clinically, respiration is likely to be almost imperceptible so that methods of evaluating the depth of anesthesia other than observation of the respiration must be relied upon. This depression of respiration is dependent upon the concentration of the drug in the blood at any one time so that large amounts may be given safely in broken doses over a period of time.[16] Fortunately, the rate of destruction of the drug given in therapeutic doses is so rapid that even though depression of respiration results in momentary arrest, breathing recurs almost before cyanosis appears. Adriani and Rovenstine[10] have shown experimentally that pentothal as well as other anesthetic agents produces a constriction of the bronchial musculature, probably through parasympathetic stimulation, which is relieved by atropine.

Weese,[198] in calling attention to a number of deaths reported during operation for sublingual infections under various intravenous barbiturate anesthetics, advances the following interesting explanation on the basis of experimental work performed with dogs. Infection in the area of the carotid sinus, which normally exerts an inhibitory effect on the respiratory center, increases the sensitivity of this structure by impairing its blood supply. Under these circumstances, the fast acting intravenous barbiturates anesthetize the central nervous system more rapidly than the carotid sinus. If the carotid sinus is traumatized by operation begun during this phase of anesthesia, such powerful inhibition of the respiratory center may result that death ensues. Weese advises that anesthesia continue for at least five minutes before the beginning of any operative procedure for infection in the neck so that sufficient time will be allowed for the anesthetizing of this portion of the vagus system.

Whereas the final disposition of pentothal in the body has never been clearly demonstrated, it has been assumed that it is detoxified in the

liver. The clinical and experimental data which have been presented as a basis for this assumption, however, have been not entirely convincing. Three cases of jaundice following pentothal anesthesia have been reported. Vaizey[189] suggested that in his case the phenomenon may have been a superimposed catarrhal jaundice; Phillips[143] reported two cases of jaundice "which might be attributed to pentothal." Several anesthetists[123, 129] report cases in which pentothal administered to patients with known hepatic damage caused prolonged periods of anesthesia. Experimental poisoning of the liver with hepatotoxins, such as chloroform and carbon tetrachloride, gives to therapeutic doses of short-acting barbiturates long-acting anesthetic action.[9]

Reynolds, Schenken, and Veal,[153, 154] after giving comparatively large doses of pentothal sodium to mice, found areas of focal necrosis in the livers of nineteen out of twenty animals, a change which also was present after nembutal anesthesia but absent after the administration of amytal and evipal. Again these authors make no mention of metabolic control or oxygenation during anesthesia. Other[30, 71, 80] investigators in experiments upon mice, dogs, and monkeys have found no liver changes other than the mobilization of glycogen and its temporary replacement by fatty infiltration, a change which occurs in all general anesthesia.

Ravdin[149] states that liver necrosis is likely to occur when any of a variety of anesthetic agents are used, regardless of the glycogen level, if the liver fat is above normal or the reserve stores of protein are seriously reduced. Since in hepatic disease there is impaired flow of blood, anoxia of the liver results easily. Adequate oxygenation minimizes this danger. It is his opinion that extensive liver damage occurs during ether anesthesia when the oxygen supply is reduced to 15 per cent, a concentration 5 per cent less than air, and that death frequently is caused by anoxemia during anesthesia. Lahey[93] states that "anoxemia is the basis of most of the anesthetic difficulties."

Scheifley and Higgins[161] called attention to the possibility that hepatotoxins may alter the central nervous system as well as the liver. An experiment was devised in which they removed 70 per cent of the liver of each of a group of nine rats and observed that the duration of the action of pentothal sodium was not influenced by this partial hepatectomy. They found also that unilateral nephrectomy did not affect the action of the drug. This method of approach would seem to obviate the objections to the use of the hepatotoxins in determining the action of pentothal upon the liver and to corroborate the clinical observations of other observers that patients with hepatic damage require full doses of pentothal sodium for narcosis.[39] This form of anesthesia has been used in cases of intense jaundice,[30] in massive carcinoma of the liver,[159] and in carefully controlled normal cases without the production of liver damage as measured by the Quick hippuric acid and bromsulfalein tests or by icterus index readings. Whereas clinical survival does not mean

that damage to vital organs has not been done, Cameron and de Saram[27] express an opinion based on experimental work that functional disturbance of the liver precedes actual damage which can be demonstrated by histologic methods. Sise[168] states his conviction concerning the effect of pentothal that "when the liver is well supplied with glycogen and when there is no lack of oxygen during and following anesthesia, liver damage need not be feared."

Marshall[121] mentions the administration of sulfanilamide as a contraindication to intravenous pentothal anesthesia. Adriani,[8] in investigations with rats to which sulfanilamide had been given, found that subanesthetic doses of pentothal became anesthetic, and that doses that were anesthetic to untreated animals were usually lethal to the sulfanilamized group. Lundy[104] reports that jaundice and general malaise have been observed clinically after the concurrent use of the two drugs. He and Adams[5] suggest that pentothal not be used within twenty-four or forty-eight hours after the administration of another sulfur-containing drug. Other writers[105, 150] have sounded the same warning. However, Nosworthy[135] and Smith[172] report the administration of pentothal to patients to whom sulfapyridine had been given in large doses without demonstrable ill effects.

Clinicopathologic observations, as reported by several authors,[30, 64, 116, 159, 186] have demonstrated no significant changes in blood sugar, nonprotein nitrogen, uric acid, creatinine, and the Quick hippuric acid tests following sodium pentothal anesthesia. Kidney function as indicated by urinalysis is not affected.[116] Mild variations in blood sugar levels have not been of sufficient degree to influence sodium pentothal's favored use as an anesthetic of choice in diabetes.[102, 207]

Experimental work to determine the minimal lethal dose of pentothal sodium in rabbits[87] and dogs[64] has proved this value to be approximately 35 mg. per kilogram of body weight, one-half of which amount gives satisfactory anesthesia. Other investigators[69, 131] using rats and cats have estimated the minimal lethal dose to be from 90 to 225 mg. per kilogram, and Gruhzit and his co-workers[56] have stated that the ratio of the maximal tolerated dose to the minimal anesthetic dose is 4.5:1 in rats and 3.8:1 in dogs. Given to rabbits in a single dose, 10 mg. per kilogram of the drug was found to be detoxified after ten minutes, 25 mg. per kilogram after thirty minutes.[87] The results demonstrate that so rapidly is the drug destroyed that the clinical use of the intermittent method allows one dose to be partly detoxified before the next is administered. This becomes especially evident when it is considered that induction of anesthesia is usually obtained by the administration of less than 3 mg. per kilogram of body weight and that subsequent doses are less than 1 mg. per kilogram of body weight. The total amount of pentothal used in an operation lasting one hour varies

between 13 and 26 mg. per kilogram. Thus theoretically there is a very safe relationship between the probable minimal lethal dose in man and the amount required for anesthesia. Carraway[30] has reported autopsies on twelve patients who died several days after operation, in none of whom was found any pathologic change which he attributed to the pentothal sodium anesthesia.

Since immediate death of experimental animals after overdosage has been demonstrated to be due to respiratory paralysis without the effect of any other pathologic process,[80, 86] it follows logically that the recommended antidotes for pentothal sodium are various respiratory stimulants such as coramine, picrotoxin, alpha-lobeline, metrazol, oxygen, and carbon dioxide.[9, 28, 30, 31, 41, 44, 64, 80, 82, 90, 94, 100, 107, 108, 116, 133, 151, 164, 188, 200, 201] These in many instances have appeared to be specific in the treatment of overdosage. A note of caution in the indiscriminate use of coramine and metrazol was sounded by Maloney,[118] who demonstrated that stimulating doses of coramine and metrazol, administered to barbitalized rabbits, caused transitory arousal at certain dosage levels, with death from depression in others; in every instance coramine or metrazol, when combined with barbital, increased the duration of narcosis over that of the controls. It would seem that these observations merit further investigation.

Picrotoxin is reported to be the most effective antidote for pentothal.[151, 201] However, with its use there is a dangerous depression of cortical activity which comes on just before the onset of convulsions.[41, 201] A report of the Council on Pharmacy and Chemistry of the American Medical Association[152] on the "Present Status of Picrotoxin in Poisoning by the Barbiturates" states that when the two drugs are given together, there is "a combined form of poisoning by picrotoxin and the barbiturate with a mixture of stimulation and depression, from which within a given range of doses the animal ultimately recovers." The report suggests that the use of picrotoxin is justifiable in cases which can be carefully studied.

CLINICAL CONSIDERATIONS

The introduction of two important improvements in the technique of administration of intravenous anesthetic drugs made it possible for pentothal sodium to become an effective agent for general anesthesia. The first of these innovations was the development of the intermittent method of administration in which the anesthetic solution is injected as the indication arises. This technique permits the maintenance of an even anesthesia, and because of the rapidity of the destruction of the drug, makes sodium pentothal anesthesia as controllable[28, 38, 80, 82, 96, 116, 138, 147, 157, 168, 191] and its use as safe as that of any inhalation anesthetic. The second fundamental improvement

in the technique of administration was the wide adoption of the continuous administration of oxygen during anesthesia. It has been shown that the barbiturates as a class affect the respiration by decreasing its depth. For this reason, adequate oxygenation during a barbiturate anesthesia can be obtained only by employing a concentration of oxygen higher than that found normally in the atmosphere. The continuous administration of high concentrations of oxygen during intravenous pentothal sodium anesthesia permits adequate oxygenation to be maintained during phases of anesthesia productive of muscular relaxation sufficient for any operative procedure.

In perusing the literature, one is impressed with the diversity of opinions concerning the scope of the usefulness of pentothal sodium. Many clinicians advise its use only for short anesthetics and in operations not requiring marked muscular relaxation.[2, 4, 28, 67, 92, 96, 107, 109, 147, 159, 188] This group lists as contraindications such conditions as asthma and cardiac decompensation, contending that abdominal operations and other procedures requiring muscular relaxation are not feasible under pentothal sodium. Still others[29, 30, 82, 137, 139, 180, 187, 191] have doubted that there are any contraindications to its use and indeed list so-called contraindications as actual indications for intravenous sodium pentothal. During the last two years, anesthetists who were at first very cautious in the use of pentothal have found wider uses for the method. This has been especially evident at the Mayo Clinic where each annual report since 1934 has shown pentothal sodium to be used in a greater proportion of the anesthetics given at that institution.[106-111, 113]

If barbiturate narcosis is carried to a stage of surgical anesthesia, respiration, although it remains regular, is insufficient in depth to supply the body with sufficient oxygen; hence a comparative anoxemia indicated by a peculiar pallor and mild cyanosis results. However, with the continuous administration of oxygen, whether by intranasal catheter, by mask, or by intratracheal catheter, this relative anoxemia is entirely eliminated, and the patient maintains a healthy color throughout the anesthesia.* The concomitant use of oxygen and pentothal sodium thus permits the maintenance of a depth of anesthesia allowing complete muscular relaxation[29, 38, 116, 120, 121, 132, 180] and makes intravenous pentothal more widely applicable in various surgical procedures. At the same time the quiet breathing is in itself a considerable advantage in that abdominal operations are complicated less by interruption from straining and forceful respiration than under almost any other form of anesthesia;[29, 30, 137, 157] this factor undoubtedly has considerable effect in increasing the speed of operation and in reducing the morbidity therefrom.

*Although no reports of its use have been seen, it is a matter of speculation whether or not a mixture of helium and oxygen might not make the use of intravenous pentothal sodium entirely safe in anesthetizing young children who with their narrow air passages have been considered not suited for this method.

Pentothal sodium is compatible clinically with all other common anesthetic agents and may be used as a supplement to local, regional, or inhalation anesthetics. Organe and Broad[137] and later Lundy and his co-workers[111] have suggested a technique by which nitrous oxide and oxygen in a fixed proportion* are used as a basal anesthetic, with the addition of intravenous pentothal sodium to secure any desired depth of anesthesia. This method furnishes an adequate oxygen supply, and the small doses of pentothal which are necessary make possible a shorter recovery period even after prolonged anesthesia. Lundy[104] reports that after induction by pentothal sodium, intratracheal intubation can be accomplished in one-third the usual time and that a much smaller amount of the inhalation anesthetic drug is then required. Guedel[57] states that pentothal and evipal, employed for the induction of anesthesia before the administration of cyclopropane, are effective in preventing cardiac arrhythmias, by virtue of their action in elevating the threshold of activity of the autonomic nervous system and the conductive mechanism of the heart.

Pentothal is finding increasing use as a supplement to spinal anesthesia[7, 61, 77, 123, 169] both to prolong the anesthesia, when the operative procedure consumes more than the expected time, and to cause unconsciousness in the patient undergoing a long operation under spinal anesthesia. Jarman,[77] who anesthetizes his patients with pentothal before administering the spinal anesthetic agent, believes that in this way he is able to reduce the incidence of backaches and headaches which frequently follow spinal anesthesia. Hand and Sise[61] state that it is their custom to administer intravenous pentothal to a patient undergoing an operation upon the stomach under nupercaine spinal anesthesia as soon as the surgeon decides to perform a long procedure such as gastric resection. They point out that muscular relaxation usually outlasts sensory anesthesia and that pentothal in small amounts will give adequate relief from pain and mental stress under such circumstances. Adams and Lundy[7] suggest light pentothal narcosis as an effective remedy for nausea occurring during spinal anesthesia.

Aside from offering a considerable margin of safety and a wide utility, a good anesthetic should be acceptable to the patient. That this is true of pentothal sodium is adequately attested by the testimony of those to whom it has been administered. Organe and Broad,[137] in calling attention to the short postoperative phase of euphoria frequently experienced, tell of the English patient who described his experience as "better than a trip to Brighton." Phillips[142] reports that it is a common experience to find a patient eating a hearty lunch within two hours

*Lundy uses 50 per cent nitrous oxide; Organe and Broad, 85 per cent nitrous oxide. While the latter authors report that the patient's color is good with the use of 15 per cent oxygen, this does not correspond with other experiences, and such a low concentration of oxygen is not to be recommended.

following operation. Lahey,[93] in giving his personal experience as a patient, calls pentothal "a delightful anesthetic."

Induction is a matter of a few seconds after the injection is begun. There is no excitement during the second stage, the patient drifting into unconsciousness as if in normal sleep. This characteristic is of especial value in the management of the hypertensive and nephritic patient.[105] Taking advantage of the rapidity and quietness of induction, the surgeon is able to shorten the period of anesthesia by preparing the field of operation prior to the beginning of the anesthetic.[29, 31] Because of the similarity of the mode of induction to the universal "blood test,"[29, 30, 85, 116, 123, 145, 159, 166] the usually apprehensive thyrotoxic patient may be put to sleep in her room without any knowledge that operation is contemplated. Long, Mickal, and Ochsner[97] have shown that the wisdom of this method of induction is reflected in the lessening of postoperative reaction in the hyperthyroid patient as indicated by lowered pulse and temperature curves.

One of the most desirable characteristics of the recovery period following intravenous pentothal is the patient's freedom from nausea and vomiting.[64] Jarman and Abel[80] reported 1,000 cases without a single instance of vomiting where preliminary medication had not been used. Cameron[28] reported 225 cases in which the only instance of vomiting followed an opiate. In Rawlings' series of 400 cases,[150] there was not a single instance of postoperative vomiting or headache. Not all clinicians have had such perfect records, but the fact seems to be established that postoperative vomiting is greatly reduced, a factor which is of immense importance as regards the patient's comfort and welfare. The acidosis associated with postoperative vomiting is a severe handicap, particularly to the diabetic patient, and makes the selection of an anesthetic drug which does not cause nausea particularly desirable in this group of patients.[140] There is also an absence of excessive sweating during the operative and recovery periods,[30, 38, 106] a characteristic which must be partially responsible for the fact that shock seems to be less than after other types of anesthesia.[96, 99, 104, 106, 116, 166] Following short operations, the length of the recovery period is extremely short, being calculated by various writers[2, 28, 107, 137] as from five to thirty minutes. Its length is approximately proportionate to the amount of the drug administered. Following the longer procedures, full recovery may be delayed for as long as six to twelve hours.[38, 137] However, even in these cases, the patient may be roused in from ten to sixty minutes,[29, 136] although, undisturbed, he prefers to sleep on. Postoperative restlessness has been reported as a rare complication[29, 49, 98, 121] with an incidence in a large series of cases of 0.05 per cent. Davison and Rudder[38] report the occasional and unexplained occurrence of hyperpyrexia during the post-

operative period, with fever of from 102° to 103° F. lasting six to eight hours, but state that they have never seen a bad result from its occurrence.

Whereas intravenous sodium pentothal is employed by some surgeons as the anesthetic of choice in all surgical procedures,[29, 30, 191] its use is limited to certain operations by others. The absence of the anesthetist and his apparatus from the region of the operative field makes the use of intravenous pentothal desirable in operations upon the head and neck, particularly in those cases in which the use of the cautery or electrosurgical unit creates a distinct fire hazard. It is reported as a desirable anesthetic by urologists,[136, 184, 186] ophthalmologists,[98] psychiatrists and neurologists,[14, 48, 51, 130, 134, 159] bronchoscopists and laryngologists;[6, 34, 121] it is used to control the convulsions caused by local and general anesthetic agents, by tetanus and eclampsia[33, 99, 102, 127, 159, 162] and to create a phase of "twilight sleep" permitting more careful investigation and treatment of personality problems.[13, 40, 67, 176*]

The elderly and the debilitated tolerate intravenous pentothal sodium especially well,[2, 5, 64, 105, 148] and it is reported as the method of choice not only in these poor risk groups but also in diabetes,[7, 102, 207] myocardial degeneration,[15, 82] asthma, chronic bronchitis, and pulmonary tuberculosis,[82, 102, 137] surgical shock,[99, 106, 116] and in patients in whom, for one reason or another, inhalation and spinal anesthetics are contraindicated.[107, 116] It is reported as the anesthetic of choice in manipulative surgery[43, 120] where the low incidence of vomiting makes it desirable in a group of patients who frequently have eaten recently.

Some of the most ardent exponents of pentothal are those men who have employed it in the field of obstetrics. Kassebohm and Schreiber[82] have reported 250 cases in which intravenous evipal or sodium pentothal was used during childbirth without the occurrence of alarming signs or symptoms in mother or child. They and other writers[31, 66, 91, 157,175, 177] have recommended it as an analgesic agent during the final stages of labor and during cesarean section. They believe this form of anesthesia to be especially suited to obstetrical practice for several reasons: it has no effect upon uterine contractions except to enhance slightly their force, a factor which is thought to shorten labor; no depression of infant respiration has been noticed; no instance of post-partum hemorrhage influenced by the drug has been observed; a state of analgesia can be deepened quickly to one of anesthesia on occasion; patients under the effect of pentothal sodium were very amenable to suggestion and cooperation was easily obtained. This last characteristic was of great value in Horsley's[66] experience in the management of childbirth in a mental hospital. The series reported by Kassebohm and Schreiber[82] in-

*It appears to be of little value as an adjunct to crime detection since subjects partially under its influence can lie or tell the truth without memory of the experience.[102]

cluded the successful management during labor of a case of status asthmaticus, one of a decompensated rheumatic heart, and a third of severe pyelitis.

Intravenous pentothal sodium is proving valuable to British anesthetists in the exigencies of military surgery.[70, 79, 124] It is of particular value to victims of chemical warfare when it is desirable to use an anesthetic agent which is not irritating to the lungs. Solutions are relatively stable for from twenty-four to forty-eight hours, and as much as 500 c.c. can be made up at once and used over that period. Because of the availability of the drug, the ease with which it is transported and administered, the short induction time and the quiet recovery, important time and energy can be conserved when one anesthetist must be responsible for numerous anesthesias in a short period.

METHOD OF ADMINISTRATION

The apparatus used for intravenous pentothal administration may be as simple as a sterile syringe and a small-bore intravenous needle. Various amplifications of these have consisted largely of apparatus for stabilizing the source of supply of the anesthetic solution. Some anesthetists employ a three-way valve which allows the continuous administration of intravenous fluids during operation with the addition of the pentothal sodium solution when indicated. Others have made use of various types of stands for holding the syringe containing the solution. It can be injected into the tubing through which normal saline solution or blood is being given intravenously, but it is said to form a precipitate when mixed with glucose solution.[61]

Preoperative sedation with a "heavy" barbiturate, an opiate, and atropine is considered generally to be desirable, although a few anesthetists prefer to use nothing besides atropine preoperatively in order to avoid undue depression during and following operation. Long, Mickal, and Ochsner[97] studied fifty patients undergoing thyroidectomy and demonstrated that postoperatively the elapsed time before recovery from the anesthetic was much shorter in those patients receiving little preoperative sedation and pentothal anesthesia supplemented by ethylene and cyclopropane than in those patients receiving a "heavy" barbiturate preoperatively and inhalation anesthesia alone. Atropine is thought to minimize excessive tracheobronchial secretions, and, by decreasing vagal tone, to act as a prophylactic agent against transitory hiccoughing, sneezing, and laryngeal spasm which have been observed infrequently during the induction of the anesthesia.[10, 30, 114, 126, 150, 165, 180, 188] The occurrence of laryngeal spasm has been attributed to the presence of mucus in the larynx[150] and to an improper speed of injection of the anesthetic drug.[114] Adriani and Rovenstine[10] in an experimental study showed that pentothal produces a constrictor effect upon the bronchial

musculature through the agency of parasympathetic stimulation, an effect which can be prevented by the prophylactic use of atropine sulfate.

The pentothal sodium is dissolved in sufficient distilled water to make the desired solution. Since it has been shown that the incidence of phlebitis in the vein receiving the solution is directly proportionate to the concentration of the drug[104] (1 case in 1,000 with the use of 5 per cent solution; 1 case in 3,000 with 2.5 per cent solution), a concentration of 5 or 2.5 per cent is usually employed for induction of anesthesia while a 2.5 or 1.25 per cent solution is used for subsequent injections.

No established dosage can be indicated because of the marked variation in individual susceptibility, but it has been stated that the necessary dosage varies directly as the muscular component of the patient.[43] The toxic or cachectic patient usually requires a proportionately smaller amount.[64] As a rule, from 4 to 8 c.c. of a 2.5 per cent solution is required for induction of anesthesia with the additional administration of 1 or 2 c.c. as the indications arise. A total dosage of 1 to 2 Gm. is usually sufficient to maintain adequate relaxation for an hour's anesthesia. The use of as much as 3.15 Gm. has been reported[159] during an anesthesia of five and one-fourth hours for a neurosurgical procedure. The depth of anesthesia is best judged by the degree of muscular relaxation which is present; anesthesia sufficient to produce abdominal relaxation likewise will cause complete relaxation of the muscles of mastication. Rivett and Quayle[157] stress the fact that even light anesthesia gives good muscular relaxation if the surgeon is not rough in handling these structures. The condition of the patient must be watched carefully by constant observation of the blood pressure, the rate and volume of the pulse, and the color of the mucous membranes and nail beds.[145] Since respiration may be all but imperceptible, Lundy[100] has devised a cotton "butterfly" which he attaches to the patient's upper lip so that the movement of air through the nostrils may be visualized. Heard[64] states that a widely dilated pupil with a fixed eyeball means momentary overdosage, while a widely moving eye with a pupil of normal size and activity indicates returning consciousness. A desirable state of surgical anesthesia is indicated by a fixed or slowly moving eyeball with a moderately dilated pupil reacting sluggishly to light.

Maintenance of ready access to an adequate supply of oxygen is essential. For this purpose the anesthetist must devise a patent airway by holding forward the jaw or by employing mechanical aids if necessary. Oxygen should be administered throughout the anesthesia by nasal catheter, by one of the several types of masks or by an intratracheal tube. After the operation the patient must be attended constantly until his reflexes return. It is usually necessary to support the jaw during a part of this period. Lundy[104] advises the continuous administration of oxygen until signs of recovery appear.

The addition of various respiratory stimulants to the anesthetic solution has been reported by several authors[28, 100, 109, 188] who have observed as much as 30 per cent increase in the respiratory rate with a concomitant increase in depth of respiration. Other anesthetists employ picrotoxin, coramine, or metrazol routinely at the end of the operative procedure. On the occasion of need for an antidote for pentothal sodium overdosage, one of these drugs may be given repeatedly intravenously in full therapeutic dosage.[28, 34, 82, 151, 152, 188, 201] The general tendency, however, is to abandon the routine use of these drugs.[109]

TABLE I

INTRAVENOUS PENTOTHAL SODIUM ANESTHESIA

Australian Medical Congress	9	Moore	500
Berkwitz	600	Murphy	100
Bourne	116	Nicholson and Sise	177
Brown and Troup	56	O'Crowley and Chmelnik	250
Bullard	718	Organe and Broad	236
Cameron	225	Payne	1
Carraway	5,963	Phillips	500
Chaney	14	Piekenbrock and Olsen	78
Cook	1	Poole and Long	25
Cooper	27	Porter	100
Davies	9	Pratt, Tatum, Hathaway, and Water	45
Davison and Rudder	1,524	Rawlings	400
Dixon	18	Rivett and Quayle	42
Drury	16	Ruth, Tovell, Milligan, and Charleroy	5,500
Fisher	175	Schindler	1
Gardner, Nosik, and Brubaker	25	Selman	50
Garofalo	1,045	Shackleford	50
Gold and Garofalo	1	Sise and Ford	146
Haskell	20	Smith	30
Heard	60	Smith	106
Horsley	2,000	Solomons	43
Hotten	1,500	Somerfield and Tovell	1
Hunt and Lundy	25,001	Thomas	3,100
Hutchison, Mitchell, and McHugh	5	Tucker	377
Jarman	1,326	Vaizey	1
Kassebohm and Schreiber	125	Van der Post	300
Knight	150	Villar Andrade	118
LaBrecque	44	Wilcox and Tovell	19
Lahey	1	Williams	4
Long, Mickal, and Ochsner	25	Woodbridge	282
Long	250	Zierold	160
Lorhan, Westphal, Grandstaff	227		
Marshall	333		
Miller and Tovell	500	Total	54,851

STATISTICAL DATA

That intravenous pentothal sodium is gaining a deserved popularity is attested by series of figures such as those from the Mayo Clinic[111] which reports that in 1940 this method was employed alone or in combination in 30.5 per cent of all instances in which an anesthetic was administered. A complete review of all the American and British literature has been made and a series of 54,851 anesthesias by intravenous pentothal sodium has been collected (Table I). Twelve deaths are re-

ported to have occurred during anesthesia, two afterward. A brief analysis of these is necessary to formulate a mortality rate.

1. Organe and Broad[137] report a death in a man, 88 years of age, whose abdomen was opened because of a ruptured peptic ulcer; this death, they state, was not due to the anesthesia.

2. Cameron[28] describes an obese diabetic patient who succumbed twenty-five minutes after the induction of anesthesia; the autopsy showed multiple cardiac infarcts.

3. Carraway[30] reports 3 deaths in his series: an elderly patient with a strangulated hernia who vomited and aspirated into the lungs large quantities of fluid during the second stage of anesthesia.

4. A negro male with a crushed hand whose death was proved at autopsy to be due to air emboli.

5. A hypertensive patient with an enormous heart who ill-advisedly was given an anesthetic and who died in the second stage of anesthesia.

6. One of Cooper's[34] patients died from massive pulmonary hemorrhage during bronchoscopy in a case of lung abscess.

7. Wilcox and Tovell[203] report the death of a diabetic patient following an operation in which intravenous pentothal sodium anesthesia was employed; however, they fail to state the length of elapsed time or whether the death was influenced by the anesthetic. It is interesting to note that the mortality in the group receiving pentothal sodium intravenously was 5.3 per cent while the mortality rate in their entire series of 236 operations on diabetic patients was 12.2 per cent.

8. Davison and Rudder[38] report "one death in which anesthesia played a part," that of a young negro with bilateral pulmonary tuberculosis who had a local anesthetic supplemented by pentothal. Four hours after operation there was a respiratory collapse and death.

9, 10, 11, 12. Jarman[78] reports 4 deaths at General Hospital during 1938 in patients, each of whom had received pentothal sodium in combination with several other anesthetic agents.

13. Patterson[140] reports 2 deaths during pentothal anesthesia. One occurred in a woman, 56 years of age, who had a long history of cardiac insufficiency and was classified as a poor risk. After she was given 5 c.c. of a 2.5 per cent solution of pentothal sodium for the extraction of a tooth, her whole body became rigid. Although her heart continued to beat for three minutes, artificial respiration was not effective because of the fixation of the patient's thorax in expiration. No mention is made of the availability of oxygen or of adequate apparatus for its administration.

14. A male patient acutely ill from Ludwig's angina was given 5 c.c. of a 5 per cent solution of pentothal sodium and the operation was begun one and one-half minutes later. The patient moved and was given another 3 c.c. of the anesthetic solution. Several minutes later he began

to have respiratory difficulty and ceased to breath, although his heart continued to beat for five minutes. This episode is similar to those reported by Weese[198] in which deaths from respiratory paralysis occurred during operations for sublingual infections in patients incompletely anesthetized with evipal.

Eliminating the cases reported by Organe and Broad, Cooper, Wilcox and Tovell, and Jarman, there remain 7 instances in which death may be ascribed to the anesthetic agent; 4 of these might have been avoided had proper facilities been available or had better preparation of the patient and better clinical judgment been used. Remarkable in this collection of 54,851 cases is the absence of any single report of postoperative pulmonary collapse or pneumonia; symptoms of milder respiratory complications were almost as rare.

Although an honest effort has been made in the preparation of these figures to avoid duplication and other inaccuracies, we do not presume that they represent an accurate estimation of the actual use of pentothal sodium. Numerous clinicians have not reported their experiences and others have done so without enumerating their patients or mentioning anesthetic mortality. Up until May, 1940, the manufacturers had distributed more than 1,800,000 ampoules in this country and in England,[1] but how much of this remains still in the hands of wholesalers and branches is not known. Likewise, the accuracy of the mortality rate which we have tried to establish undoubtedly will not stand the test of larger series, but will serve for the present to point the risk which this method entails.

As in the use of all other types of anesthesia, the greatest danger to the patient lies in the administration of intravenous pentothal by inexperienced anesthetists. This point is made poignantly again by Jarman[78] who, in collecting the 1,300 anesthetic deaths reported between 1921 and 1939, found that 80 per cent of the fatalities occurred with house officers in charge, whereas only 8 per cent of the reported deaths were among patients managed by full-time anesthetists. Lahey,[93] Lundy and Tovell,[106] and Ruth, Tovell, Milligan, and Charleroy[159] reiterate this warning for those who would use intravenous pentothal sodium. However, numerous writers, among whom are Jarman and Abel,[80] Kassebohm and Schreiber,[82] Lundy and his associates,[113] Mallinson,[116] Murphy,[132] and Thomas,[180] attest the safety of this agent when used by a cautious and skilled anesthetist who has at hand adequate equipment.

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Review of Recent Meetings

MEETING OF THE UROLOGICAL SECTION OF THE SOUTHERN MEDICAL ASSOCIATION, ST. LOUIS, MO., NOVEMBER 12 AND 13, 1941

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THE Urological Section of the Thirty-Fifth Annual Meeting of the Southern Medical Association met November 12 and 13, 1941, in St. Louis. The following program was given:

1. **Renal Cortical Necrosis: Case Reports, Fred K. Garvey,** Winston-Salem, N. C.—Forty-two cases of this entity were reported in 1934 and forty-seven additional cases have been recorded in the last seven years, showing it is of clinical importance. While there are exceptions, it occurs typically in pregnant multiparas over 35 years of age and is characterized by renal pain, nausea and vomiting, edema, anuria, and death. The anuria, which is the most striking symptom, comes on suddenly after delivery in a patient with no previous urinary abnormalities. Cystoscopic examination, including retrograde pyelography, is negative. The etiology is unknown, but the pathology consists in a thrombosis restricted to the terminal lobular arteries of the kidney with coagulation necrosis of the renal cortex. Garvey has seen three cases, all following delivery. The first patient was anuric for seventeen days before death. In the second, the N.P.N. reached 200 mg. per 100 c.c. of blood before death on the tenth day. The patient in his final case passed no urine for five days before dying. These cases showed normal pyelograms; autopsy revealed the cortical necrosis.

In the discussion, **J. C. Pennington,** Nashville, Tenn., reported a case in a newborn simulating this malady. Another discussant felt that probably some cases diagnosed as eclampsia are actually cases of renal cortical necrosis.

2. **The Technique of Pyelography, H. McClure Young,** Columbia, Mo.—Young presented his method in detail, the essentials of which are the use of a 10 c.c. piston syringe and slow injection of the pyelographic medium with cessation of injection at any facial expression of discomfort by the patient. He does one side at a time. He emphasized the necessity for cooperation by patient, x-ray technician, and doctor.

J. U. Reaves, Mobile, Ala., and **H. K. Wade,** Hot Springs, Ark., reiterated that gentleness is the watchword in pyelography. They felt there was no valid objection to making a bilateral pyelogram on the same plate. **H. M. Spence,** Dallas, stated that air pyelograms were not used as generally as their value would warrant. In a fairly extensive experience with the method, he has been convinced of its safety and value, particularly in stone cases. Also in the dispensary patients, it had an economic advantage because the flat plate and pyelogram could be combined on one film.

3. In a **Symposium on Conservative Renal Surgery, R. B. McIver,** Jacksonville, Fla., spoke first on **Plastic Procedures for the Correction of Defective Renal Drainage.** He confined his remarks to the surgical correction of significant ureteropelvic obstruction and presented clear-cut motion pictures of his technique. In a series of 100 such cases, he carried out conservative operations as follows: (a) disposal of fibrous bands, adhesions, and aberrant vessels, 70 cases; (b) plastic operation

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on the ureteropelvic junction for stenosis (Y-plasty of Foley and others), 20 cases; (c) resection of renal pelvis and reimplantation of ureter, 10 cases.

McIver stated the purpose of all these operations was to refunnel the pelvic outlet. He demonstrated many valuable technical points, including the use of a "blowout patch" of fat to seal a defect rather than an overabundance of sutures; the use of a nephrostomy tube and ureteral catheter splint for ten days to three weeks after the plastic and the reimplanting operation; the necessity for complete lysis of adhesions, bands, and vessels at the junction, after which, if obstruction still remains due to stricture, a plastic must be done; the combining of a nephropexy to provide suitable postural drainage along with the corrective operation; and finally systematic cystoscopic dilatation and lavage in subsequent treatment.

Next **Louis M. Orr, Jr.,** in association with **P. R. Kundert,** Orlando, Fla., discussed **Renal Counterbalance in Relation to Conservative Renal Surgery.** Orr reviewed Hinman's theory of counterbalance, which states that, granted a normal kidney and a hydronephrotic kidney of sufficiently long standing so that its function has been assumed by the normal kidney, anatomic relief of the hydronephrotic kidney will not be followed by its functional recovery. Orr presented a personal case in substantiation of Hinman's theory in which satisfactory anatomic regression of a hydronephrotic kidney following a plastic procedure was not accompanied by recovery of function. A moderate hypertension developed also. Orr concluded that the ability of a hydronephrotic kidney to recover could be tested by retention catheters and functional tests. Perhaps nephrectomy might be preferable in some cases rather than conservative surgery.

Thomas D. Moore, Memphis, Tenn., presented **Late Results in Plastic Surgery in Hydronephrosis.** Factors involved in the choice of cases for this type of surgery include the age and life expectancy of the patient, the possibility of future childbearing, the economic status, the ability to clear up or control urinary tract infection, and the type of obstruction.

In 18 cases (2 bilateral) of noncalculous hydronephrosis operated upon by Moore and followed for from seven months to ten years, there was no operative mortality; the ages were from 7 to 70 years; there were 2 failures with subsequent nephrectomy and another developed a stag-horn calculus six years after operation. Best results were obtained in 10 cases of high insertion of the ureter, where only 1 failure occurred. In 6 cases of aberrant vessel, section of the vessel alone in 6 instances was disappointing.

Moore said a word in favor of the Rammstedt incision for ureteropelvic junction stricture. He had found reimplantation of the ureter gratifying. Long nephrostomy drainage and splinting (e.g., six weeks) was advocated in some cases.

In general, late results of conservative surgery were 80 per cent good and 20 per cent unsatisfactory.

Discussion of this symposium settled largely around the question of counterbalance. **C. E. Burford,** St. Louis, and **R. E. Van Duzen,** Dallas, questioned its clinical application. In regard to the conservative surgery, Van Duzen would prefer to do a plastic procedure, but if it were not feasible, he personally would do a nephrectomy rather than attempt reimplantation.

4. **Ureterointestinal Implantation: Experimental and Clinical Results With a New Method, Hugh J. Jewett,** Baltimore, Md.—The operation is carried out in two stages. Stage I: Abdomen opened in midline; ureters freed up from pelvic brim downward; each buried in a furrow along the corresponding side of the sigmoid and abdomen closed. The ureters are not severed and the urinary stream is not diverted. Stage II: After two weeks or longer, abdomen reopened; ureters distal to implantation severed and segment attached to bladder tied and allowed to retract; a special insulated electrode devised by Jewett is inserted into open end of implanted ureter, current applied and electrode plunged into bowel; end of ureter now treated as appendix stump by burying in bowel wall.

Jewett has done the operation in numerous dogs and several human beings. Excretory urograms and autopsy specimens attest to the value of the method in avoiding sepsis and constriction of ureteral opening.

H. A. O'Brien, Dallas, evaluated the method favorably as combining the best features of several preceding methods. His only theoretical objection was that the final opening in the ureter was in its lateral wall rather than its open end.

5. **Sulfathiazole Therapy in Venerology, A. A. Creecy** and **H. L. Switkes,** Newport News, Va.—Creecy reviewed an extensive experience with hospitalized young males in which various dosage schedules were used. The diagnoses included gonorrhea, nonspecific urethritis, and chancroid. He concluded that the drug was very effective in all these conditions. Large initial and total doses in the hospitalized group were somewhat more effective than moderate doses. Sulfathiazole blood level determinations were not particularly helpful. Creecy has had opportunity to study sulfadiazine also, and he feels that sulfathiazole is somewhat more toxic than sulfadiazine but no less efficacious.

7. **Preoperative Use of Sulfathiazole for the Prevention of Postoperative Complications: A Clinical Study, J. A. C. Colston,** with **R. W. Satterthwaite,** Baltimore, Md.—In spite of all the usual precautions, infection still remains a hazard in operations on the genitourinary tract. It has occurred to many that having a sulfonamide concentration present in the body at the time of operation might prevent the growth of bacteria already present and the ingress of others following the operation. Thus Hugh Young and his co-workers have reported on the preoperative use of sulfathiazole in fourteen plastic operations on the genitals in which it was evident that healing occurred more quickly and with less danger of sepsis.

In order to determine the value of sulfathiazole administered preoperatively as a prophylactic against postoperative complications, Colston, over the past eighteen months, used the drug routinely in a series of 112 urological cases where infection was already present or where the urinary tract was to be opened and compared the results with a corresponding control series in which the drug was not used. A dose of 2 to 4 Gm., averaging 3 Gm. a day, was administered for a preoperative interval of forty-eight hours, including a dose on the morning of operation. Colston felt this dosage and interval gave a maximum protective effect with a minimum of toxicity. The postoperative temperature chart was used as the index of morbidity.

In the group which had received sulfathiazole preoperatively, the temperature reactions were consistently lower in the first four postoperative days than in the control series. This was particularly noteworthy on the third and fourth days, when elevated temperature means serious sepsis. Furthermore, no pneumonia or blood stream infection occurred in the sulfathiazole-treated series in distinct contrast to the control group.

8. **Oswald S. Lowsley,** New York City, was the guest speaker, selecting as his subject **Plastic Operations in Urology.** He presented many illustrated cases. For exertional incontinence in women, he has modified the classic Kelly operation of plicating the base of the urethra and bladder neck by making an incision superior to the external meatus and plicating the roof of the urethra with ribbon catgut. He has similarly plicated the perineal musculature and rectal wall through a perineal exposure in a few cases of incontinence of urine and feces due to spina bifida with good results. He stated that ribbon catgut contains only ⅙ as much catgut as the ordinary twisted variety and possesses the additional advantage of not cutting out of delicate musculatures; it is ultimately replaced by fibroblasts.

For undescended testicle, Lowsley uses a modified Torek procedure in which, after lengthening the cord as much as possible by meticulously dissecting away all fibrous bands, adhesions, etc., he replaces the testicle in the scrotum and uses

a traction suture of catgut passing through the gubernaculum or lower pole of the testicle out through the scrotal sac and being tied to the skin of the thigh. This suture absorbs in a week or so after all danger of retraction of the testicle has passed. He described a case of cryptorchidism in which he found the testicle in the neighborhood of the kidney and was able to bring it down to its normal position after severing all blood supply except the artery of the vas and the vas itself, and have the testicle remain viable. This fortunate result is a marked exception to the general rule.

Lowsley reported 15 per cent success in his hands of Hagner's operation of anastomosing the vas to the upper pole of the epididymis in cases of sterility due to occlusion of the genital passageways following epididymitis.

Lowsley gave follow-up results of the operation he has devised for impotence, which consists of plicating the ischiocavernosus and bulbocavernosus muscles with his ribbon catgut through a perineal incision. Of 143 cases, he was able to follow personally, 67 per cent were considered successful, 22 per cent improved, and 11 per cent unchanged. The most suitable cases for operation are the ones following some traumatism to the perineum. In the individual with atrophied perineal musculature, subsequent to early hypersexual activity, it is also indicated. He was emphatic in his insistence that this is not an operation for old men or psychoneurotics and should be done only after exhaustive preoperative study and observation.

A motion picture showing Lowsley's operation for hypospadias was presented. This is well illustrated in his recent textbook. He has treated approximately fifty cases by this method with good results. He prefers to do the procedure shortly before puberty. Some idea of the patience required in this type of case is shown by a patient on whom seventeen separate operations were necessary before an ultimate excellent result was achieved.

9. **Grayson Carroll,** St. Louis, delivered the Chairman's Address entitled **Urological Investigational Work in the South,** in which he summarized the original investigations in all fields of urology by the membership. In answer to questionnaires sent out to twenty-five representative members, he found that adequate facilities exist for investigational work, but most men met the expenses of their investigations wholly or in part out of their own pockets. Carroll pointed out the advantages of having endowed research institutes, including funds from commercial firms and foundations supported by royalties from medical patients, to make further investigations. He urged urologists to use their influence in appropriate ways to found institutes for research.

10. **Jarratt P. Robertson,** Birmingham, Ala., spoke on **Renal Injury,** presenting his observations on 26 cases. The series included 25 males and 1 female. Causative factors included: automobile accidents, 12; penetrating wounds (knives, gunshot, ice pick), 6; falls, 3; football injuries, 2. The pathology varied from contusions to lacerations and frank rupture. The predominant symptom was hematuria, which was present in over 90 per cent of the cases, while shock, renal pain and tenderness, and injuries to other viscera were noted frequently.

In regard to diagnostic measures, Robertson favors cystoscopy and retrograde pyelography as most valuable in showing early the extent of the damage and laying the basis for proper treatment. He feels that the excretory urogram is not of much value in these cases due to suppression of urine from the attendant shock and impaired renal secretion and that the dangers of sepsis following cystoscopy and retrograde examination have been exaggerated.

Robertson emphasized that the treatment depends on the general condition of the patient as regards shock, associated injuries, and the extent of the renal damage shown on retrograde pyelography. He recommends trying conservative treatment first, including bed rest for two weeks after cessation of the hematuria. Frequent checkups are necessary in cases treated conservatively. His rule in the

kidneys necessitating operation is to save the patient first and if possible the kidney. Twenty of Robertson's cases were treated conservatively and 7 by operation, including 2 late nephrectomies. He had 4 deaths, 2 being operative cases and 2 nonoperative cases where severe shock contraindicated surgery.

11. **Diagnosis and Treatment of Traumatic Rupture of the Posterior Urethra, C. J. Reynolds,** Bluefield, W. Va.—Reynolds emphasized the value of using the Foley catheter as a splint for the damaged urethra and to pull the severed bladder neck downward. The bladder is opened through a suprapubic incision to facilitate the manipulation and placement of the catheter but is then closed.

12. **Torsion of the Testicle and Its Appendages, Hubert K. Turley,** Memphis, Tenn.—Turley presented 4 cases illustrating this condition. In 1 case of recurrent torsion, he was able to save the testicle and perform an orchiopexy. In 2 other cases, orchidectomy was necessary. In 1 case of torsion of the hydatid of Morgagni, excision of this appendage with preservation of the testicle was done.

Turley emphasized the fact that torsion of the testicle is a surgical emergency if the testicle is to be saved and he urged calling this to the attention of pediatricians. He mentioned the differential diagnosis between torsion and epididymitis (sudden onset of torsion, absence of urinary infection in torsion, pain exaggerated on elevating testicle in torsion; i.e., Prehn's test). It is probable that torsion is not recognized as often as it should be.

The treatment is immediate surgical exploration and detorsion; if the blood supply is not impaired, the testicle is saved and fixed to the scrotum to prevent a recurrence. If blood supply is compromised, orchidectomy is done. Papers 10, 11, and 12 were discussed by **Edgar Burns,** New Orleans, La., who reported a series of 16 cases of torsion from Charity Hospital, in which 9 orchidectomies were necessary. He felt the clinical picture was the important factor in kidney injuries and determined the course of procedure. **Rubin Flocks,** Iowa City, Ia., emphasized the importance of late observation and urography in cases of renal injury.

13. **Wm. C. D. McCuskey,** Wheeling, W. Va., presented **A Résumé of the End Results of 1,000 Consecutive Cases Following Surgery for the Relief of Bladder Neck Obstruction,** extending over the years 1930 to 1941 for his own practice. This series included 958 adult males, 17 children, and 15 women. The indications for surgery included 772 cases of benign hypertrophy, 185 carcinomas, and 27 "cord" bladders. Seventy-five "prophylactic" resections were done. A total of 900 transurethral resections were performed, 60 patients requiring two or more sessions. Originally the Caulk punch was used in a series of 243 cases with 4 deaths, but now the McCarthy resectoscope with the Bovie electrosurgical unit is employed for the transurethral work. Radical total perineal prostatectomy was done in several cases after tissue removed by resection showed carcinoma.

From the follow-up of this wealth of material, McCuskey concluded that the operation should be selected for the patient and not vice versa. His results in transurethral resection in Grade IV hypertrophies left something to be desired and he felt that the suprapubic operation entailed no greater risk than two or more resections in this type of case. He was not favorably impressed with the "prophylactic resections." He felt that the use of the resectoscope detected more early carcinomas and broadened the opportunities for total perineal extirpation.

In the discussion, **J. F. Patton,** St. Louis, stated that the aims of bladder neck surgery were (1) to restore function with (2) a low mortality and it was often necessary to strike a balance between the two. It was his belief that 20 per cent of these cases were since best handled by open operation.

H. L. Tolson, Cumberland, Md., stated that a minimum of coagulation led to better results.

Book Reviews

The Treatment of Burns (Oxford War Manuals). By A. B. Wallace. Pp. 113, with 16 illustrations. London, Humphrey Milford, 1941, Oxford University Press. $1.25.

This book is the product of the traditional home of advanced thought concerning burns in Scotland—the Royal Hospital for Sick Children and the University of Edinburgh. The important work on burns carried out by Mr. W. C. Wilson during the decade 1928 to 1938 has been continued by the author of the present volume since Mr. Wilson's appointment as Professor of Surgery at the University of Aberdeen. An adequate discussion of the early care of burns followed by insufficient data regarding subsequent plastic management is a weakness inherent in many works on burns. Such is not the case with Wallace's book as he shows evidence of his intensive training in plastic surgery received under Sir Harold Gillies as a part of the British war effort. The book adequately considers all chronologic aspects of the care of a burn case.

Inclusion of diagrams of emergency instrument tables and of practical lists of materials needed for treatment is of value from the standpoint of war use. The nursing care of burns is adequately considered. This is an important item in cases of emergency when large numbers of burns may overwhelm the capacities of the medical staff.

The book begins with chapters on the classification, clinical course, and complications of burns, after which the remaining four-fifths of the material is devoted to treatment itself. The use of tannic acid is not abandoned while indications for more recent treatments such as the Bunyan envelope and the triple dye are listed. The local use of sulfonamide drugs, first described in Great Britain by Wallace himself in an article (Brit. M. J. **1**: 469-472, 1941) appearing just as this book went to press, is described in the present text.

One objection to the book might be the space given to special consideration of burns in children. This would seem to be out of place in a war manual, but when it is remembered that in total warfare civilian burns are not infrequent, this objection is not so valid. The book seems to be a succinct review of the present status of burn treatment, and should be of interest to civilian, industrial, and military surgeons.

Anus, Rectum, Sigmoid Colon: Diagnosis and Treatment. By Harry Ellicott Bacon, B.S., M.D., F.A.C.S., F.A.P.S. Ed. 2. Pp. 857, with 487 illustrations. Philadelphia, 1941, J. B. Lippincott Co. $8.50.

The second edition of this well-known book gives the medical profession a detailed and comprehensive treatise of all those structures and lesions coming within the preview of the proctologist. In some instances, the strict confines of proctology have been overstepped. Excellent discussions of malignant tumors of the sigmoid colon are included. For this reason, the book is enhanced in value and will be appreciated the more by the general surgeon. No fewer than sixteen different operative procedures for dealing with malignancy of the rectum and sigmoid colon are described. The more common lesions of the anus and rectum are considered in detail in all their phases.

The format of the book makes for easy reading and ready reference. The 487 illustrations, which include diagrams, drawings, and photographs, are excellent. Lengthy bibliographies are included at the end of each chapter and cover the world literature up to 1939. A detailed index, both of the authors quoted and subjects covered, is appended.

Without doubt, this book will become a standard and authoritative source in its field.

Hemorrhagic Diseases: Photo-Electric Study of Blood Coagulability. By Kaare K. Nygaard: Pp. 320, with 59 illustrations. St. Louis, 1941, The C. V. Mosby Co. $5.50.

In spite of recent intensive investigations there still exists a lack of trenchant knowledge on the subject of hemorrhagic diseases. This is clearly indicated by the varied and, in many instances, confusing classifications of the multitudinous hemorrhagic manifestations. Obviously investigations which may aid in clarifying some of these problems must be considered desirable. Accordingly this monograph is a distinct contribution.

Realizing that not the least important factor contributing to the confusing character of hemorrhagic diseases has been the lack of reliable procedures of investigation, Nygaard has approached the problem by concentrating on the measurement of the velocity of blood coagulation. This has been accomplished with the application of the photo-electric principle which permits a more dependable method of study. The author has applied this investigative procedure to various hemorrhagic diseases and has compiled in this book his results and interpretations.

The book is divided into three parts, the first of which is devoted to a brief review of the various approaches to the measurement of blood coagulation and a description of the photo-electric principle and particularly its applicability to the problem of blood coagulation. The second part is divided into three chapters. In the first of these there is presented the results of certain experimental investigations on factors which may influence the coagulability of blood plasma. In the second chapter the author gives a brief review of the prevalent opinions concerning the nature of the thrombin-fibrinogen reaction and an interpretation of his observations with the photo-electric principle. A brief review of the character and mechanism of the coagulant effect of thromboplastin and the author's investigations of this subject with the photo-electric principle are presented in the third chapter. The third part of the monograph includes six chapters, the first of which is devoted to another classification of hemorrhagic diseases. The results of the author's studies and his interpretations as well as brief reviews of hemophilia, thrombocytopenic purpura, vitamin K deficiency, the hemorrhagic tendency in diseases of the biliary tract, liver, and pancreas, and hemorrhagic disease of the newborn comprise the other five chapters. Since these are not the only conditions which may be considered in the group of hemorrhagic diseases, the criticism that the title is misleading may be applied. Apparently, however, the author's purpose was not a complete review of the subject of hemorrhagic diseases but rather an exposition of this new approach of investigation and an interpretation of the results of his observations in the more common forms of these diseases. In this respect the book is a distinct and commendable contribution to the subject, and deserves careful consideration particularly by investigators interested in the varied and bewildering disturbances of blood coagulation.